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VOLUME 28 JUNE 1961 No. 6

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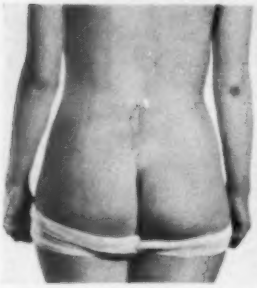

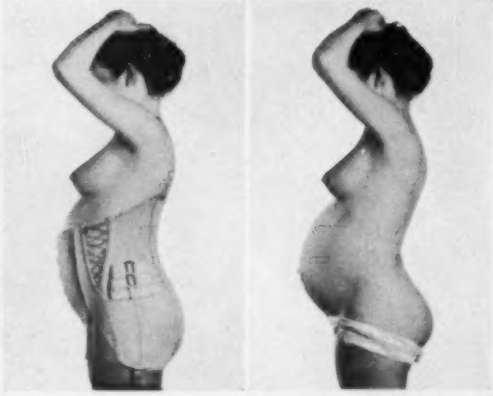

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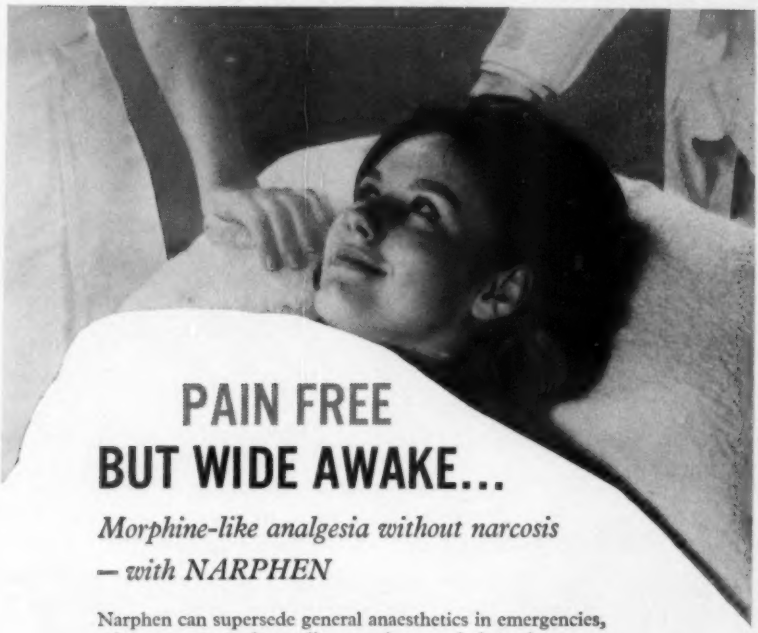

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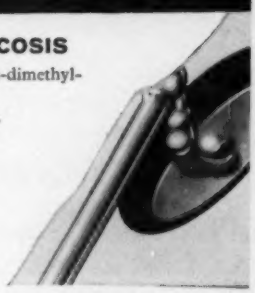

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JUNE 1961

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MALIGNANT MELANOMA

Bradshaw Lecture delivered at the Royal College of Surgeons of England

on

7th December 1960

by

Sir Stanford Cade, K.B.E., C.B., F.R.C.S., F.R.C.P., F.R.C.O.G.

Vice-President of The Royal College of Surgeons,
Consulting Surgeon, Westminster Hospital

IT IS MY privilege to-day to deliver the 78th Bradshaw Lecture. This privilege is conferred by the President, and I thank the immediate past President, Sir James Paterson Ross, for adding my name to the list of Bradshaw Lecturers, a distinction awarded in rotation, usually by seniority, to every member of the Council fortunate to survive long enough to become the Senior Vice-President.

Although, therefore, I cannot feel any personal sense of achievement in addressing you to-day as the Bradshaw Lecturer for 1960, I am specially pleased to do so and this for several reasons.

Firstly because William Wood Bradshaw was a product of my own Hospital. Born 159 years ago in Bristol, he received his medical education at the Westminster Hospital, and practised as a general practitioner surgeon at Andover and later at Reading. The Lecture was endowed by his widow in 1866, 14 years after his death, as a testimony of her gratitude for the happiness she owed him. Simultaneously, she endowed a similar eponymous lecture at the Royal College of Physicians.

The first Lecture was delivered by Sir James Paget on 13th December 1882, and he described Bradshaw as " a home-loving and studious man who diligently cultivated his mind in both literature and science ".

There is no need to recount in detail the known facts about his life, as these have been mentioned in many previous Bradshaw Lectures. But the names of some previous lecturers are of interest; they include after Sir James Paget, Lord Lister, Jonathan Hutchinson, Spencer Wells, Henry Butlin, Rickman Godlee, Bland-Sutton, Moynihan, all giants in surgery in their time.

In the 78 years since the foundation of the Bradshaw Lecture to commemorate the name of a Westminster man, there has been only one Westminster surgeon before me to become a Bradshaw Lecturer. That lecture was delivered on 8th November 1923, and I was present on the occasion in the old lecture theatre since destroyed by enemy action.

I would like to pay tribute to the Bradshaw Lecturer of 37 years ago—Walter George Spencer (Fig. 1), then Senior Surgeon to Westminster Hospital. Born 102 years ago in Wiltshire, the son of a farmer, he entered the medical school of St. Bartholomew's Hospital in 1881. He was as

brilliant in surgery as he was erudite in classics and literature. He was closely associated with Butlin and was a co-author with him in 1885 of a text-book on *Diseases of the Tongue*; he worked with Sir Victor Horsley, made original observations on the physiology of the brain and gained the Jacksonian Prize in this College in 1889 on " The Pathology, Diagnosis and Surgical Treatment of Intracranial Abscess and Tumour ". His Vicary Lecture in 1922 on Vesalius remains a classic for all time. He served the College as a member of the Court of Examiners for ten years and a member of Council for eleven years; he was Hunterian Professor, Arris and Gale Lecturer, Erasmus Wilson, Vicary and Bradshaw Lecturer; he was Chairman of the Library Committee, Assistant Editor to d'Arcy Power

Fig. 1. Walter George Spencer, M.S., F.R.C.S., Bradshaw Lecturer R.C.S., 1923, Senior Surgeon, Westminster Hospital, and Vice-President, Royal College of Surgeons (1858–1940).

in the production of the latter's *Lives of the Fellows*. He wrote two text-books on surgery in association with Walsham (1903) and Gask (1910); he translated from Latin the three volumes of Celsus' *De Medicina*.

But his main life's interest was Westminster Hospital, then in Broad Sanctuary opposite Westminster Abbey (Fig. 2). There he spent his active life as a surgeon from 1887 till his retirement in 1923, and it is there that he found the material for his Bradshaw Lecture, entitled " Melanosis, Melanin, Melanoma and Melanotic Cancer " (Fig. 3). My association with Spencer extended over a period of 25 years, till his death in 1940.

It is Walter George Spencer's example and precept which influenced me in the choice of subject for this Lecture. The concluding sentence of his Lecture was truly prophetic: " The general bearing of recent observations suggests the hope that further chemical research may arrive at a

means of controlling the disease by therapeutic measures", anticipating chemotherapy of malignant melanoma by a quarter of a century.

There are, however, two additional reasons why I chose malignant melanoma as the subject of this Lecture. It has become very nearly traditional for the Bradshaw Lecturer to deal with a subject in which he has had exceptional experience and I can at least claim that the choice of subject fulfils this desideratum. But, in addition, the last will and testament of Mrs. Sally Bradshaw, a fascimile of which appears in Sir Zachary Cope's lecture for 1949, stated that she wished to maintain her husband's name in good repute by associating it with the advancement of the science which he loved. I think there is considerable advancement in our

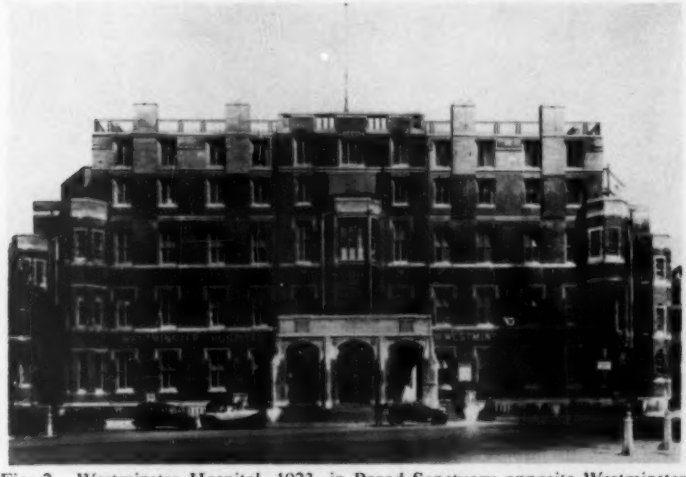


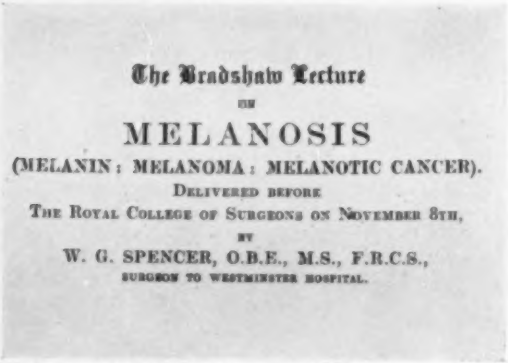
Fig. 2. Westminster Hospital, 1923, in Broad Sanctuary opposite Westminster Abbey.

knowledge of the management of malignant melanoma, but, unfortunately, the advances have not reached the majority of practitioners, and I feel impelled to use this opportunity to attempt to influence the treatment of this affliction which in the hands of many still leaves much to be desired.

It is not the lack of warnings which seems to prevent a number of doctors, hospital residents and surgeons from treating this condition by incorrect methods.

The indifferent management of many patients with malignant melanoma is not new. In 1939 Grey Turner states: "Having taken an eager interest in the subject of malignant melanoma throughout the whole of my life, I know only too well that the vast majority have died of that disease", and he adds: "But in practically all cases the treatment has been totally inefficient." In 1944 Margaret Tod, of the Holt Radium Institute,

Manchester, wrote on "The Tragedy of Malignant Melanoma." She began her article in the *Lancet* by an appeal to the heart: "There is no greater tragedy in medicine than the death from multiple metastases of a young patient, who has been in perfect health until a small pigmented mole was removed for cosmetic reasons"; and she records a series of 34 patients who died as a result of meddlesome and incompetent treatment. "Some of the expressions used by patients," she writes, "give a vivid picture of the careless way these dangerous lesions were handled. 'It was nipped off'; 'he tied a string round it'; 'he cut the top off'; 'he touched it up with caustic'; 'he gouged it out'. Such words are sufficient proof that the deplorable treatment was given without any thought as to the nature of the condition treated." Such statements by patients are not echoes from the past, they can be heard to-day in hospital out-patient clinics.



The Bradshaw Lecture

ON

MELANOSIS

(MELANIN: MELANOMA: MELANOTIC CANCER).

DELIVERED BEFORE

THE ROYAL COLLEGE OF SURGEONS ON NOVEMBER 8TH,

BY

W. G. SPENCER, O.B.E., M.S., F.R.C.S.,

SURGEON TO WESTMINSTER HOSPITAL.

Fig. 3. W. G. Spencer's Bradshaw Lecture, *British Medical Journal*, 17th November 1923.

In 1930 James Ewing drew attention to the fact that "familiarity with these apparently insignificant lesions constantly invites meddlesome interference by patient, surgeon, dermatologist and other specialists". In 1949, B. Sylvén, of the Radiumhemett, Stockholm, stated: "Great harm was done by doctors, chiropodists and beauticians who treated early cases of malignant melanoma by freezing, caustics, electric needling."

Four years ago, from a review of 132 patients seen at Westminster Hospital (Cade, 1957), I pointed out that the initial or first treatment was of vital importance, and I made a strong plea that no patient should be submitted to minor excisions, biopsies followed by delay before treatment is undertaken, or other interference, as these result in a negligible chance of survival. Since then my series of cases has increased by nearly a hundred patients, and still it is a common experience to meet patients in whose treatment every canon of our surgical creed and every surgical principle in the treatment of cancer is lightheartedly broken. Pigmented

lesions continue to be excised both in doctors' surgeries and in out-patient departments of hospitals under local anaesthesia, inadequately, and not infrequently the specimen is thrown away and with it the slender chance of the patient's survival.

The natural history of malignant melanoma

Observation of large series of malignant melanoma reveals the frequency of these lesions in the blond individual and those with red hair, and in the pale complexioned. Most patients with malignant melanoma do not know how long the lesion has been present, and the commonest answers given by patients are " as long as I can remember ", " all my life ", " since childhood ", and not infrequently " I do not know ". In the majority of patients there can be found other pigmented skin lesions, most frequently the so-called " common mole " or the pale " café au lait " patch and the soft pigmented fibroma.

The benign pigmented lesions are extremely common, and when present usually multiple, their numbers varying from a dozen to several hundreds. In contrast with the frequency of benign lesions is the rarity of malignant melanoma, estimated to be 3 per cent. of all skin cancers. A minority of malignant melanoma are said to arise *de novo* and in fact appear as new lesions, not by transformation of a pre-existing benign mole. But a closer study of the histology, specially the method of local spread, seems to indicate that even the melanoma apparently arising *de novo* is in fact a metaplasia in an occult, pre-existing dermal naevus.

The pre-existing mole should therefore be considered as possessing potentialities of metaplasia, and deserves closer study. In the past 25 years, the interest of pathologists has shifted from the speculative as to the origin of the naevus cell to the descriptive of the various histological types. The focussing of attention on the histogenesis of these tumours dates from 1948, and the contribution to the understanding of the pathology of malignant melanoma, and hence the rationale underlying the principles of treatment, are due to Arthur Allen (1949) and Sophie Spitz (1948, 1951), who showed genius in the painstaking care taken in the study of the unrivalled clinical material at the Memorial Hospital, New York. They analysed the clinical data of 934 patients with malignant melanoma and reviewed the histology of the primary lesions in 337 cases.

A critical understanding of the clinical course and of the histological characteristics of benign pigmented lesions is essential to the understanding of the malignant melanoma and its management.

Allen and Spitz's classification (1953) of the benign pigmented lesions into five groups is now generally accepted and will be very briefly reviewed. The benign lesions are classified into five groups: (1) the intradermal naevus or common mole; (2) the junctional naevus; (3) the compound naevus; (4) the juvenile melanoma, and (5) the blue naevus (Fig. 4).

The Intradermal Naevus, as implied by its name, is situated entirely in the dermis, the epidermis is intact although atrophic in places; it is never encapsulated and the masses of naevus cells extend down to, and often penetrate into, the subcutaneous fat. It is the commonest variety, mature and stable; the " hairy mole " is of this type. It should be noted that the

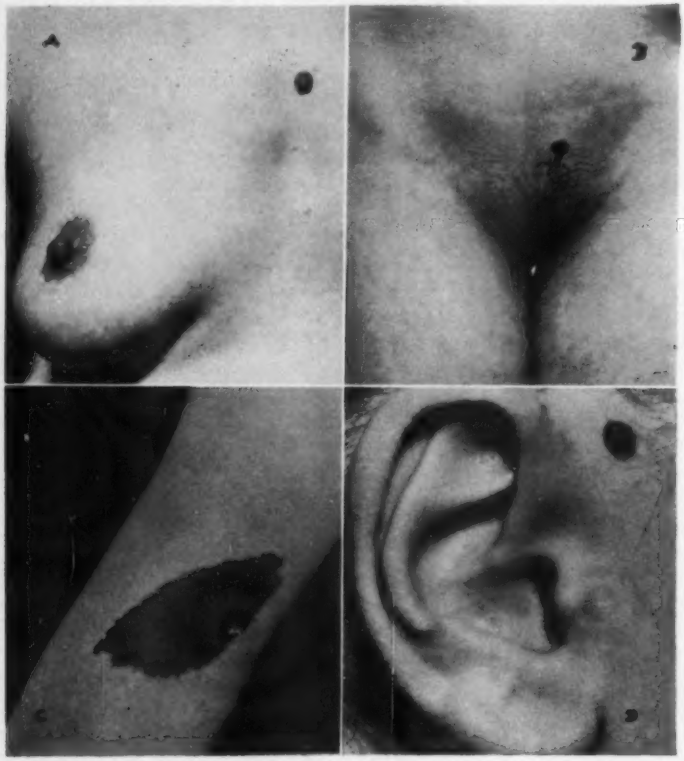


Fig. 4. Benign pigmented lesions. A. Intradermal naevus in a patient 40 years of age. B. Junctional naevus in a patient 11 years of age. C. Compound naevus in a patient six years of age. D. Blue naevus in a patient 11 years of age. All these are benign. All should be removed by local excision. Scars are safer than pigmented moles. In children their removal should be done before puberty.

intradermal naevus does not occur on the palm of the hand, the sole of the foot or the genitalia; lesions on these sites, therefore, should be presumed to be other than intradermal naevi. The intradermal naevus is benign and remains benign. Its removal is dictated on cosmetic grounds and local limited removal is all that is needed. It is therefore wrong to postu-

late that these benign lesions should not be removed as interference may result in a malignant metaplasia. Clinically, the lesions vary in colour from light to dark brown; they vary in size from one millimetre to several centimetres; they are flat and smooth or papillary, warty and hairy. All hairy moles are of this type. The loss of hair over a mole indicates activity, and signifies the presence of other than dermal elements.

The Junctional Naevus. It is so named as histologically it can be seen in the basal layer of the epidermis at its junction with the dermis. This type spreads through all the layers of the epidermis and may reach the surface. A point of very great practical importance is the nature of its peripheral spread. At the edges, the main mass may be separated from minor collections of marginal groups of cells by normal epidermis, and thus an apparently complete surgical removal showing normal epidermis beyond the naevus may be misleading. These areas, called " skip areas " by Allen (1949) and Allen and Spitz (1953), explain the appearance of local recurrence after what seemed to be a complete removal. The junctional naevus is " immature ", potentially unstable, may become active and undergo metaplasia into a malignant melanoma. Histological changes of activity are recognized by nuclear anaplasia, hyperchromatism, increase in nuclear size, subepithelial lymphocytic infiltration and the presence of mitotic figures. In an adult patient these changes are precancerous; in children, before puberty, such changes have no sinister significance. The colour of junctional naevi, as in the intradermal mole, varies from light to dark brown. All pigmented naevi on the palm of the hand, the sole of the foot and external genitalia are of this type. Their removal is no longer a question of cosmetic appearance; their removal is definitely indicated. It is known that they may remain quiescent till puberty and the optimum time for their removal is before puberty. There is no evidence that their removal precipitates malignant changes. The true explanation of recurrence and dissemination following their local removal is that such lesions had already undergone malignant changes when local removal was undertaken. One should, however, look at this histological interpretation of the junctional naevus with a sense of proportion. Not all junctional naevi become malignant melanoma; in fact only a very small proportion do so. Nevertheless, it is important to remember, as Allen and Spitz (1953) are at pains to point out, that " with the exception of a few malignant blue naevi, every malignant melanoma of the skin or mucous membrane arises from a junctional naevus, or the junctional element of a compound naevus ".

The Compound Naevus. This term defines those lesions composed of two elements: junctional and dermal. Clinically these naevi are indistinguishable from the intradermal ones. In children, 98 per cent. of pigmented moles are compound; in adults only 12 per cent. are compound.

It is the junctional element of a compound naevus which renders it potentially dangerous.

The Juvenile Melanoma. It is now well known that a pigmented skin lesion occurring before puberty may have histological features closely resembling or even indistinguishable from malignant melanoma, and yet pursue a benign clinical course. This discrepancy between histological findings and the natural history of the lesions attracted much attention. In 1948 Sophie Spitz, under the name " Juvenile Melanoma ", described the precise histological features and presented convincing evidence of its benign character. Since then, much evidence of the existence of the " juvenile melanoma " as a definite entity has become available. McWhorter and Woolner (1954) reviewed all the cases previously diagnosed as malignant melanoma in children at the Mayo Clinic, and found 11 patients whose subsequent benign course supported Spitz's observation. Since then, many such cases have been reported.

The occurrence of a true malignant melanoma in children is very rare; in the present series of 226 patients only three cases were observed. It is important to recognize the existence of juvenile melanoma as it influences treatment and in the pre-pubertal patient conservative surgery, that is a limited local excision, is indicated. Pack (1948) describes these lesions as " pre-pubertal melanoma ". This variety may occasionally persist after puberty, and is found in adult life, when it is very nearly always mistaken for a malignant melanoma.

The histological characteristics of the juvenile melanoma are the presence of both elements of the compound naevus, junctional and intradermal, the occurrence of large fusiform spindle-shaped cells, the giant cell with a single or double nucleus, the epithelioid cell, the abrupt transition between the conglomeration of these cells and the intact epidermis. The clinical appearance of these lesions does not differ from the other benign pigmented lesions; it is generally small, from one to three centimetres in diameter, often oval in shape. The commonest site is the face, but these lesions may be found on the trunk and the limbs. It is a matter of interest to speculate on the fate of untreated juvenile melanoma. Allen and Spitz (1953) are of opinion, by inference from the sharp drop of incidence after puberty and from the increasing rarity of the lesion with increasing age, that it is " fair to assume that there is a tendency for juvenile melanoma to acquire, after puberty, the histological characteristics of simple intradermal naevi ". There is a similar tendency of the compound naevus to become an intradermal naevus after childhood.

The occasional persistence of " juvenile melanoma " in adult life led to criticism of this term. Helwig (1955) and Kernen and Ackerman (1960) suggest these lesions should be labelled " spindle cell naevi and epithelioid cell naevi ".

The Blue Naevus. The commonest site of the blue naevus is the face, the dorsum of the hands and feet and the buttock. It is a dark blue or black smooth hairless lesion; the skin over it appears to be tightly stretched and thinned. It is entirely intradermal, heavily pigmented with melanin. It is composed of spindle cells arranged in whorls or fascicles and its neurogenic origin is likely. It remains benign in all except a very few cases.

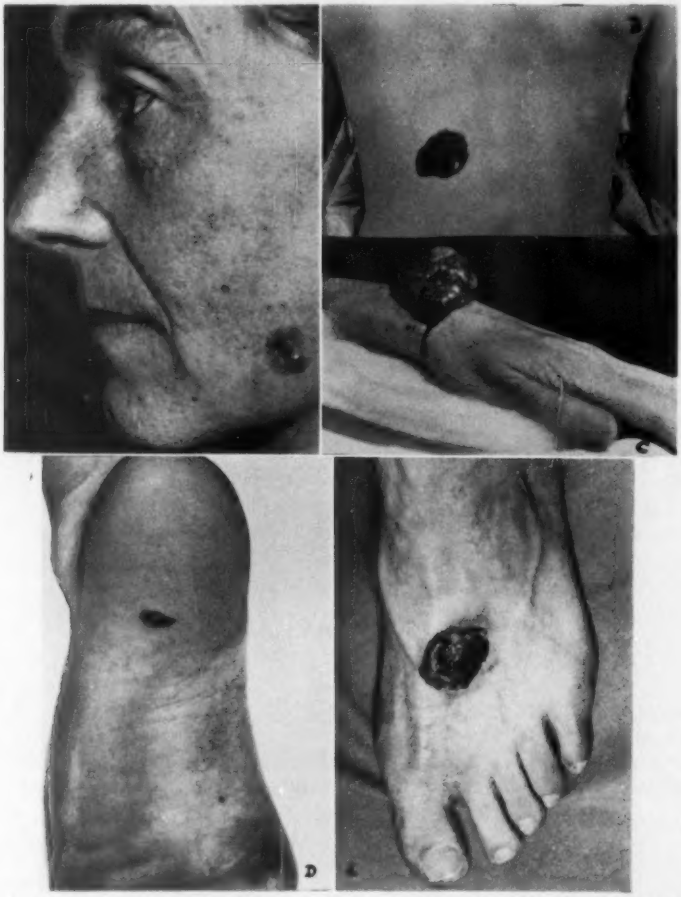


Fig. 5. Malignant melanoma. A. Lesion on face showing peripheral " halo ". B. Lesion on back, increasing in size and depth of pigmentation. C. Rapidly growing, bleeding, fungating black mass on dorsum of hand. D. Lesion on sole of foot; the patient did not know how long it had been present. E. Lesion on dorsum of foot, ulcerating and bleeding.

THE MALIGNANT MELANOMA

The histological diagnosis of advanced malignant melanoma presents no difficulty. Its characteristics are dermal and epidermal invasion, cellular pleomorphism, nuclear increase in size and anaplasia, abundance of mitosis and lymphocytic infiltration. The histological diagnosis of the early, small malignant melanoma does, however, still present difficulty; specially is this the case in what Allen and Spitz (1953) called " superficial melanocarcinoma ". They record that " even when the pathologist suspects this early or small lesion to be malignant, the diagnosis of it is often made with equivocation, to the understandable bewilderment of the surgeon ".

The clinical signs of " activity " in a pre-existing mole, and the signs of malignancy in a recently noticed pigmented lesion, are the formation of a " halo ", a staining of the skin at the periphery of the lesion, an increase in size in surface and in volume, increase in the depth of colour or a change from brown to black (Fig. 5). These changes may be noted for several months or even for one or two years before the patient seeks advice. Later, with the invasion of the superficial layers of the epidermis, there is oozing, crusting and finally bleeding on very slight trauma. Some malignant melanoma are of florid growth and form very large black, friable, cauliflower-like tumour masses. The degree of pigmentation at this stage may decrease and in some patients all pigment is lost and in some metastases the tumour masses are completely devoid of pigment.

It should be remembered that, even in the very dark pigmented black lesions, there is always the possibility of a differential diagnosis and that a variety of dark lesions bear a superficial resemblance to malignant melanoma, namely the pigmented basal or squamous cell carcinoma of the skin, the sclerosing angioma, which in young patients closely resembles the blue naevus, the pigmented senile wart, the papillary acanthoma.

THE STIMULUS TO NEOPLASTIC CHANGE

In a critical analysis of the common beliefs and teaching of the causes which stimulate a quiescent pigmented lesion to undergo a malignant change, two factors should be considered: hormonal and traumatic. Both seem superficially to be causatively related to the metaplasia of a benign into a malignant lesion, and in the melanomata admittedly in a degree of malignancy more virulent than in most tumours.

Hormonal influence

A number of natural, clinical and experimental observations show clearly a relationship between pigmentation, both normal and pathological, and hormones. These can be summarized as follows: (1) the rarity of malignant melanoma in children, and the benign course of juvenile melanoma before puberty; (2) the increase in the number of pigmented lesions and increase in size of lesions and increased pigmentation, in

children the bearers of moles, with the advent of puberty and regression of such lesions when puberty is passed; (3) the " chloasma gravidorum " of the later months of pregnancy manifested by pigmentation of the areola, axillae, groins, midline of abdominal skin, the vulva and sometimes the face, and the loss of the increased pigmentation at the end of pregnancy; (4) the inability of eunuchs to become suntanned; (5) the distribution of pigmentation in Addison's disease, which corresponds accurately to the areas of increased pigmentation in pregnancy with the exception of the areola and the genitalia; (6) the depigmentation following administration of cortisone in Addison's disease.

Experiments in frogs, tadpoles and fishes have proved abundantly the effect of the adrenals and pituitary on the formation and lack of formation of pigment.

A simple experiment described by Lerner, Shizume and Bunding (1954) shows the inhibitory effect of cortisone on the pigmentation of frogs kept in the dark: those treated with cortisone fail to pigment when kept in the dark, as do all controls.

Experiments on man could not be carried out with any ease till the pituitary factor which darkens the skin, the melanocyte stimulating hormone of the pituitary (M.S.H.), became available. Using this factor in very large doses on normal human volunteers and in the treatment of certain conditions showed clearly the effect of the pituitary and of the adrenals in pigment formation in man. Lerner, Shizume and Bunding, of Portland, Oregon, investigating the mechanism of endocrine control of melanin pigmentation, report the results of these experiments. Following the administration of very large doses of M.S.H., increased pigmentation occurred in a normal white man; in a negro woman with vitiligo, generalized marked increased pigmentation occurred, but the areas of vitiligo on the face remained apigmented, thus showing the effect on pre-existing melanocytes and illustrating the essential need of the final target organ for the formation of pigment. Increased pigmentation following large doses of M.S.H. was obtained in a patient previously adrenalectomized for metastatic breast cancer, and considerable darkening of the skin followed the administration of M.S.H. to a patient with hypopituitarism.

The experimental use of M.S.H. clarified the mechanism of pigmentation. The normal cycle is the production of M.S.H. by the pituitary and the stimulation by it of the melanocyte. Administration of cortisone and A.C.T.H. inhibits the production of M.S.H. by the pituitary and lowering of adrenalin and noradrenalin excretion facilitates the action of M.S.H. on the melanocytes. In pregnancy there is an increase of M.S.H. production and increased inhibition of the adrenals but to a lesser degree. In Addison's disease the output of M.S.H. is increased as the function of the adrenals is lowered.

Do these experiments support the belief that in pregnancy there is activation of existing malignant melanoma? Or a greater liability for metaplasia in quiescent lesions? A critical evaluation of the known physiological processes, and clinical observation of patients, shows in fact that the belief that pregnancy increases the risk by stimulating existing malignant melanoma or tends to initiate a malignant change in a pre-existing quiescent lesion is erroneous. Recent series of cases, including a review of 415 patients at the Memorial Hospital, New York (George, Fortner and Pack, 1960), shows that there is no evidence of increased spread during pregnancy, and that the clinical course in the series of pregnant patients with malignant melanoma is essentially similar to that of a control group of non-pregnant patients. In the series of 226 patients seen at Westminster Hospital, there were only eight pregnant patients: of these two are alive, free from disease for six years; three died of the disease; one could not be traced and two are alive free from disease for one or two years.

This small series, statistically insignificant, does, however, show that prolonged survival in malignant melanoma associated with pregnancy can be achieved, and that the survival rate is similar to that of all other patients. A clinician cannot fail to be impressed by the virulent course of the disease with rapid dissemination and early death from malignant melanoma in pregnancy should such a case occur in his practice; yet an exactly similar hurricane course is seen in non-pregnant women and in men. The belief that pregnancy adversely affects the course of malignant melanoma is based on single case reports and not on a comparative statistical study of a series of pregnant and non-pregnant patients.

The modern trend is to regard the physiological phenomenon of pigmentation concomitant with pregnancy as affecting the degree of pigmentation of melanoma, benign or malignant, but not the degree of malignancy of the malignant melanoma or its liability to metastasize. The specific hormonal influence on pigment formation does not affect the neoplastic process. Allen expresses it graphically: " The regulation of pigmentation is as different from direct cellular participation in the formation of melanoma, as a bricklayer is from bricks." This is, of course, in marked contrast with the effect of pregnancy on breast cancer. Hormonal influence other than that of M.S.H. may be related to malignant melanoma but is at present undetermined.

It is known that spontaneous regression and remission of disseminated malignant melanoma during pregnancy and after delivery does occur (E. P. Allen, 1955), but instances of spontaneous regression without the added factor of pregnancy and in men are also recorded (Sumner, 1953; Levison, 1955; Sumner and Foracker, 1960). It has also been shown statistically by L. P. White (1959), and noted by others, as well as in this series, that the number of prolonged survivals in women with malignant

melanoma is proportionally greater than in men, suggesting that hormonal fluxes do not adversely affect the prognosis.

The practical importance of these observations lies in the implications as regards treatment. There is no indication for termination of pregnancy in malignant melanoma, but neither is pregnancy a justification to alter the radicalism of the treatment indicated in a similar non-pregnant patient.

The advice that women who had had a malignant melanoma should avoid pregnancy does not seem to have any rational basis; in one of my patients there occurred three pregnancies during and after treatment for malignant melanoma, and this patient is alive six years after treatment.

There is, nevertheless, an inhibitory hormonal factor in the pre-pubertal patient as the occurrence of malignant melanoma is extremely rare in children and is evidenced by the observation that the most unstable pigmented lesion, the junctional naevus, is the commonest in children. There is obviously a difference between the absence of hormonal stimuli and the effect of such stimuli. Finally, no hormonal treatment by steroid compounds, nor the removal of the ovaries, adrenals and the hypophysis, have been known to achieve regression of malignant melanoma, although some lesions may become apigmented following hormonal treatment. There is therefore sufficient indication for a re-orientation of the previously widely held views, specially as regards the management of malignant melanoma in pregnancy.

The influence of trauma

The doctrine of *noli me tangere* is still fairly widespread, both among doctors and patients. The belief that the removal of a benign mole may result in dissemination with explosive violence is at the base of much unsound advice still given by doctors. Margaret Tod (1944), already quoted in the introductory part of the Lecture, in her paper on " The Tragedy of Malignant Melanoma," gives a graphic description of the disasters following interference with malignant melanoma, yet she misses the point completely and proffers advice which is against the evidence. She arrives at the erroneous conclusion that all moles which are quiescent should be left, as their removal for cosmetic reasons may be followed by dissemination, and she gives 34 examples. Pack (1959) calls this doctrine most dangerous, and to wait till a pigmented lesion becomes active is far too often to wait too long for treatment to be effective.

There is no evidence that trauma, whatever its kind, has the power to transform a benign pigmented lesion into a malignant melanoma. The belief that the frequency of malignant melanoma on the feet is due to the trauma of ill-fitting shoes is not supported by evidence. It cannot be proved or disproved, but it is known that most lesions on the feet are junctional naevi and that junctional naevi are the precursors of malignant melanoma. Why all lesions on the plantar aspect of the foot and toes should be junctional is unknown.

The tragedy of melanoma lies in the inadequate treatment of established but unrecognised malignant lesions; it should not be confused with the treatment of benign pigmented lesions, the removal of which is one of the best examples of cancer prophylaxis. Occasionally trauma is brought forward in medico-legal cases as a reason for compensation or other

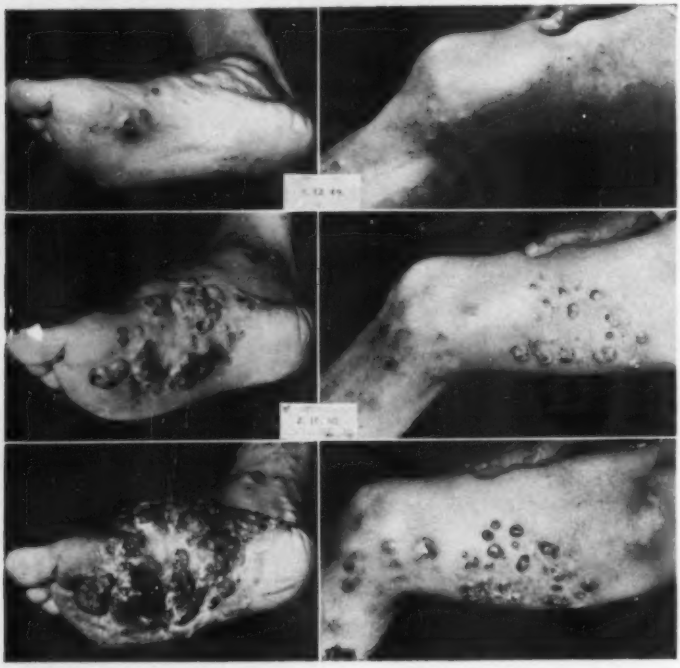


Fig. 6. The natural history of the untreated lesion showing progressive increase in number, size and pigmentation of the primary malignant melanoma on the sole of the foot and the metastatic spread by lymphatic permeation and finally involvement of inguinal lymphnodes.

pecuniary rewards such as pensions and attributability in personnel of the armed forces. In such cases there is only a presumption that trauma caused the lesion, but no proof of it.

Inadequate treatment of any malignant tumour often leads to its rapid recurrence, rapid spread and wide dissemination; this applies to malignant melanoma perhaps with greater force than to other tumours. There is a vast amount of evidence that when a benign pigmented lesion is removed locally but completely it never recurs, and that it is the mistaken diagnosis

of a malignant melanoma for a benign lesion which is followed by widespread disease if the removal is incomplete.

Mode of spread of malignant melanoma

The clinical manifestations of the spread of the disease are seen very clearly in the untreated patients, which even to-day are seen from time to time (Fig. 6), and more commonly in the patients whose disease has not been controlled either because of the inadequacy of the treatment or because treatment was given too late.

Fig. 7. Malignant melanoma on forearm, above the wrist. Spread by lymphatic embolism. The primary lesion is quite small and "quiescent"; the axillary lymphnodes are massively involved.

Spread of malignant melanoma occurs by lymphatic permeation (Fig. 6), lymphatic embolism (Fig. 7) or by the bloodstream (Fig. 8).

Lymphatic permeation produces satellite nodules: a crop of nodules spreading centrifugally both proximally and distally in the vicinity of the primary growth and gradually at increasing distances from it (Figs. 6 and 15). It occurs along the subcutaneous and subfascial network of lymph vessels.

Embolic spread along the lymph vessels gives rise to metastases in the regional lymphnodes, the intervening areas escaping local spread (Fig. 7). Either one or other of the lymphatic methods of spread occurs; sometimes both develop simultaneously or one follows the other.

Blood-borne dissemination may manifest itself by a solitary lesion or by multiple metastases which show no special tissue or organ predilection; but no tissue or organ is immune (Fig. 8).

No other malignant tumour is so unpredictable in its mode of spread and dissemination; neither the time interval nor the mode of spread can be

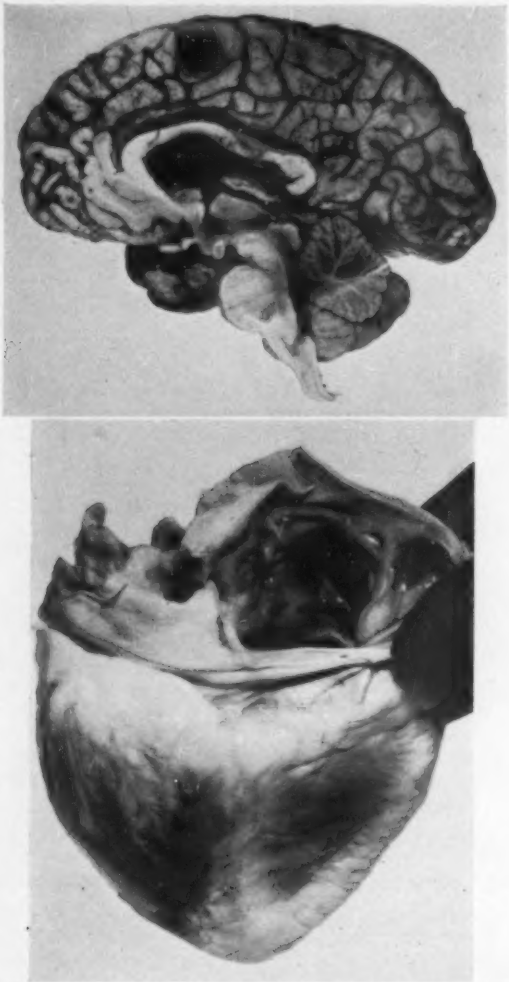


Fig. 8. Metastases in brain and heart. The primary malignant melanoma was on the leg.

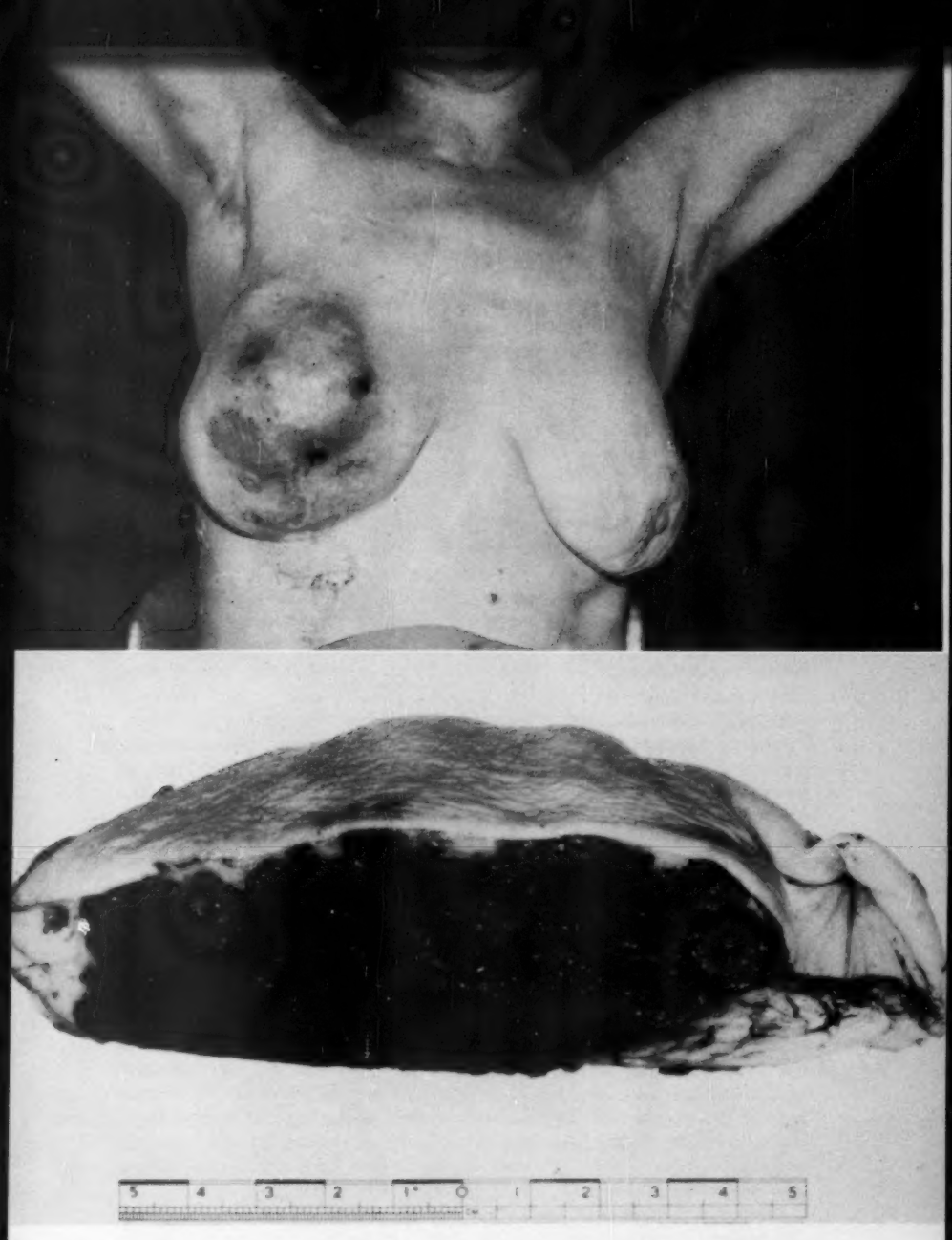


Fig. 9. Metastases in both breasts. The primary malignant melanoma was in the nasal septum. The right breast, which was oozing ink-like discharge, was amputated as a palliative measure. The breast was filled with a jelly-like inky black mass,

forecast. It is this unpredictability which renders the treatment so difficult. A solitary intracranial metastasis has been mistaken for a primary cerebral tumour; there are two such cases in this series, and not till the tumour was revealed on craniotomy was its true nature recognized. In such cases the primary malignant melanoma may be quite small, symptomless, and may have been present for months or even years, without increasing in size; or the removal of a small " mole " for cosmetic reasons several years previously may have been forgotten by the patient till he is reminded of it by direct questioning. Occasionally there is spontaneous regression of a small primary tumour followed at various intervals of time, months but more often years, by metastatic lesions, without any local recurrence. Insignificant small primary lesions may run a devastatingly rapid course or the primary tumour may rapidly become a florid mass of considerable size and yet not give rise to metastases.

Dissemination of explosive violence sometimes overwhelms the patient with a simultaneous manifestation of metastases in the liver, spleen, lungs, bones, and on post-mortem examination metastases are found in the heart, the pituitary, adrenals, kidneys, testes. A not infrequent site of metastases in women is the breast (Figs. 9 and 10) and ovary, and in these sites it is nearly always bilateral.

Primary malignant melanoma of the mucous membrane or muco-cutaneous junction arising in the mouth, the nasal mucous membrane, the urethra, vaginal introitus and the perianal region, run a more rapid course. In this series ten patients developed a primary malignant melanoma in the mucous membrane; all but the recently treated ones have died, although one has survived with disease for five years and another for nearly ten years.

Spontaneous regression

Spontaneous regression and remission have been reported. A patient known personally to me ran the following course: a primary malignant melanoma was removed from the front of the leg; metastases occurred in the inguinal lymphnodes and were excised; an operation for intestinal obstruction revealed a solitary pigmented polypoid metastatic tumour in the small intestine and the affected segment of the gut was resected. Following this there appeared a crop of subcutaneous metastases near the scar of the excision of the primary growth, in the leg and in the thigh; these, however, slowly regressed without any treatment, leaving pale, thin scars; the patient was alive and clinically free from detectable disease four years later.

Although the course of the disease is unpredictable in an individual case, the general pattern of its course is by dissemination *via* the lymphatics or the bloodstream, and often malignant melanoma cells can be demonstrated in the bone marrow or in the peripheral blood long before there is any clinical evidence of metastases. Only in the terminal stages does

melanin occur in the urine, the discoloration of the urine and the dark mahogany colour of the skin preceding death by a few days or weeks.

Treatment

Surgery, radiotherapy and chemotherapy have each an important part to play in the management of the patient with malignant melanoma. The decision as regards the choice of method and technique, or a combination

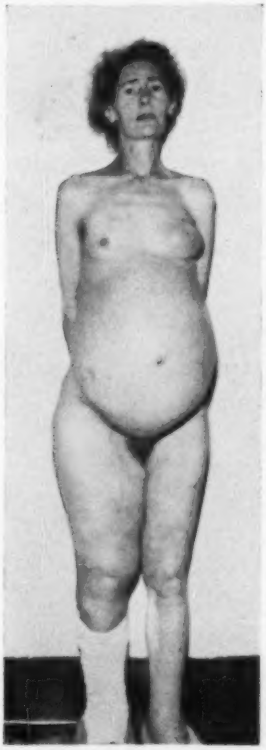


Fig. 10. Widespread metastases in liver, ovaries, left breast, inguinal lymphnodes. Gross oedema of right thigh and ascites. The primary lesion on the right leg was inadequately removed and no further treatment given.

of methods and the sequence of their use, depends foremost on the stage of the disease when the patient is seen. The rationale of the method depends on the extent and site of the lesion in the light of the natural history of the tumour and on a critical consideration of the likelihood of success of any particular method of treatment. Adequate treatment

requires courage on the part of the clinician and fortitude on the part of the patient.

Treatment of the primary growth

The diagnosis of malignant melanoma can often be established on clinical grounds. If in doubt biopsy is indicated; in small lesions this should consist of the removal of the entire lesion. Immediate frozen section histology is essential. *If facilities for this are not available, and a definite diagnosis cannot be established within 24 hours, the lesion should not be interfered with and the patient referred to a hospital where the necessary facilities are available.* Delay of two or three weeks between biopsy and radical removal is responsible for the failure to control the disease in a great number of patients.

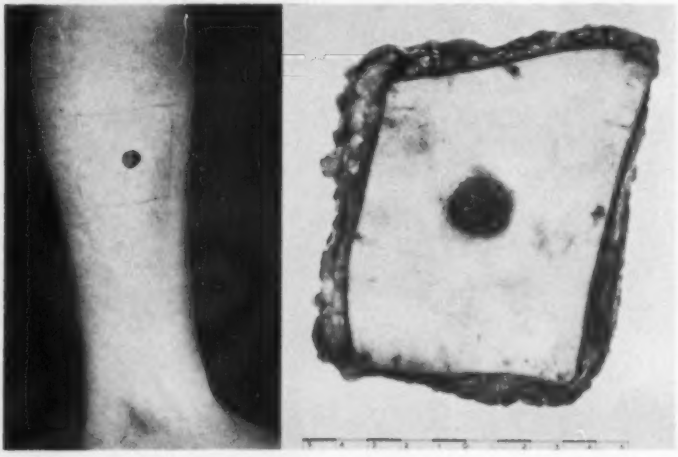


Fig. 11. Malignant melanoma, right leg. To illustrate the extent of removal considered to be adequate. This always needs a skin graft to close the defect.

The excision of a primary malignant melanoma must be wide in extent and in depth; it is in fact a tri-dimensional removal and should include in depth the subcutaneous tissue and fat and the deep fascia (Fig. 11). In surface, extent of the removal will depend upon the size of the lesion, but must be wide enough to include any junctional naevi in the vicinity and the removal of the so-called " skip " area.

Such wide excisions necessitate skin grafting to close the defect, with very few exceptions when the site of a very small lesion permits repair by a Z-plasty or a rotation flap. In the case of a limb the skin graft should be taken from the contralateral limb or the trunk, and never from the ipso-

lated limb; unfortunately this is still practised, even by otherwise experienced surgeons. It is also advisable to take the skin graft before embarking on the wide local excision.

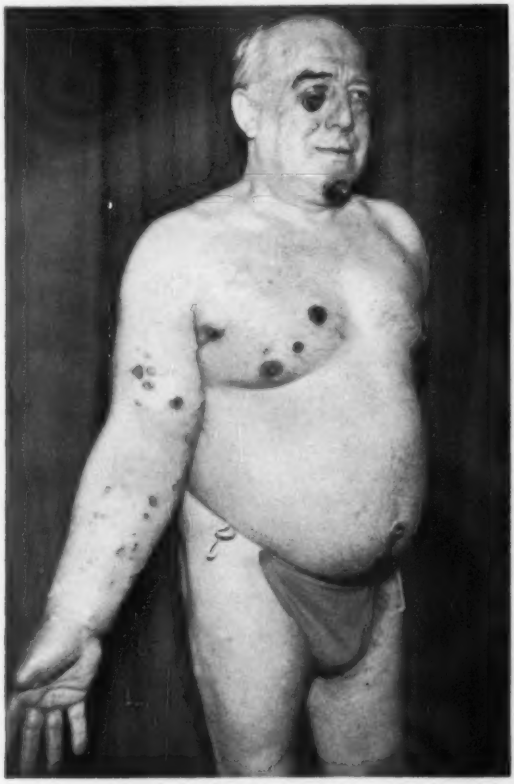


Fig. 12. The result of " inadequate " initial treatment. A subungual melanoma was first " curetted ". Local recurrence was treated by amputation of part of the thumb. Axillary lymphnodes were " scratched out " through a small incision. This patient illustrates the tragedy of " inadequate " treatment.

In the case of a subungual melanoma of the toes and fingers, the melanotic whitlow of Jonathan Hutchinson, removal of the nail and curettage or amputation of the terminal phalanx should be condemned and never practised; in such cases the finger or toe with its metacarpal or metatarsal bone should be removed (Fig. 12).

The management of the lymphnode area

In the absence of clinically detectable lymphnodes, a so-called " prophylactic " block dissection is indicated only if the site of the primary melanoma submitted to wide local excision permits the regional lymphnode block dissection to be done in continuity (Figs. 13 and 14). In the presence of palpable but operable lymphnodes, such a " monobloc " removal of the primary growth and lymphnodes is imperative. Cases suitable for this technique are lesions on the face, ear, scalp or neck; pectoral or scapular or axillary areas; lesions in the upper part of the front of the thigh, the lower part of the abdominal wall, the external genitalia. Lesions situated centrally on the back or on the abdominal wall present further difficulties and bilateral axillary or inguinal lymphnode dissection is sometimes unavoidable.

Local excision of lymphnodes, as opposed to a radical so-called "block", is meddlesome interference and should not be undertaken. Where an inguinal lymphnode dissection is indicated it should include the lymphnodes on the external, internal and common iliac vessels (Fig. 13). A block dissection of inguinal lymphnodes limited to the upper part of the thigh is not merely inadequate but quite useless and should not be practised.

A radical clearance of the axillary lymphnodes (Fig. 14) needs a good exposure which is best achieved by the removal of the pectoral muscles as in a radical mastectomy. Retraction of the pectoral muscles does not give the necessary access for an adequate clearance of the lymphnodes from the first interspace laterally. Attempts at removal of the axillary lymphnodes through a small axillary skin incision and preservation of the pectoral muscles is invariably followed by local spread of the disease and should not be practised.

When the primary lesion is situated on a site remote from the main regional lymphnodes, such as the foot, ankle, calf, fingers, hands, wrist, forearm, a lymphnode dissection in continuity cannot be achieved. The intervening distance of perhaps two to four feet between the primary site and the lymphnodes, usually to become involved, precludes an adequate excision of the primary growth, the regional lymphnodes and the intervening lymphatic vessels. Consideration of the anatomy of the lymph vessels shows networks surrounding the circumference of the limbs, subcutaneously and subfascially; a network of innumerable lymph channels. The removal of a strip of skin, as advocated by Grey Turner in 1939, seems, therefore, a haphazard procedure, which is either unnecessary or, if disease is present, irrevocably dooms the patient to numerous recurrent nodules along the entire length of the incision (Fig. 15). This procedure, because of the high esteem Grey Turner was held in, has been blindly accepted, has found its way into textbooks on operative surgery, loyally but uncritically copied from edition to edition, and is only now beginning to lose its undeserved reputation. A number of patients with a malignant

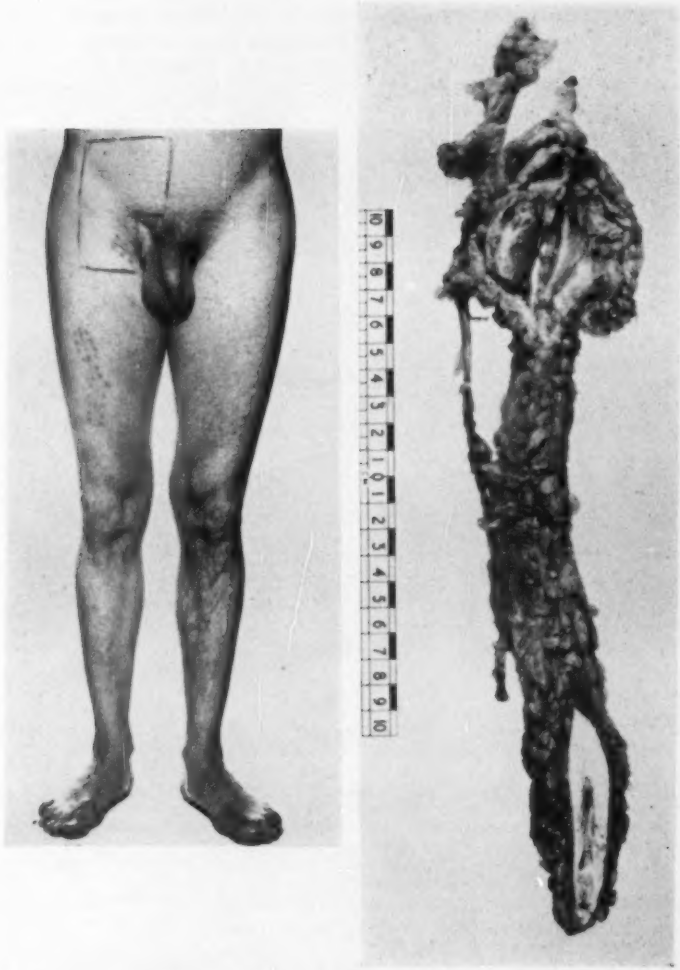


Fig. 13. The illustration on the left shows the stigmata of inadequate excision. A linear scar on the front of the thigh without a skin graft. A futile, small, horizontal inguinal incision for the removal of one lymphnode, the seat of a metastasis. The illustration on the right shows the principle of " adequate " treatment: a monoblock re-excision of the original scar and a radical block dissection of the inguinal, external iliac and internal iliac lymphnodes. The inguinal lymphnodes show gross metastatic involvement.

melanoma on a toe or finger have had the toe or finger amputated and a block dissection of the inguinal or axillary lymphnodes done in discontinuity, only to watch with dismay the appearance of a few, then several, then innumerable nodules along the entire limb from foot to groin, or hand to axilla, and from there, without any restraint, to the neck, chest, and abdominal wall (Figs. 12 and 15).

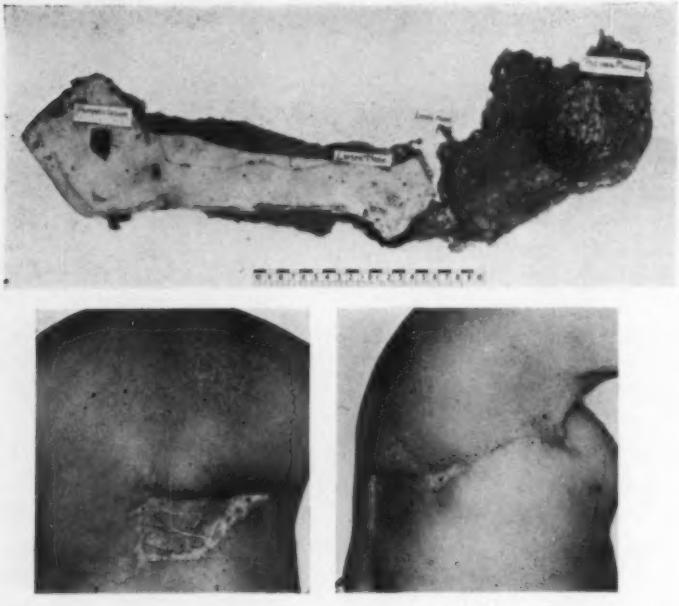


Fig. 14. Specimen of monoblock excision in continuity of the local recurrence in scapula area and the axillary lymphnodes. Every surgical principle in the management of malignant melanoma was disregarded. The primary lesion was locally excised (the wound is shown broken down), the axillary lymphnodes were " scratched " out through a small incision. The specimen shows the extent of the excision. The lower illustration shows the scar and the skin graft. The patient remains free from recurrence to date three-and-a-half years after excision.

It is true that the so-called " elective " block dissection, that is in the absence of clinically detectable enlarged lymphnodes, in discontinuity does yield from time to time the unsuspected discovery of microscopic lymph-node metastases. It would seem, therefore, that such an " elective " or clinically " prophylactic " block dissection is justifiable even if it is in discontinuity, yet the final five-year survival of such cases at the Memorial Hospital (Pack, 1959) is only 20 per cent., and the possibility of spread

by lymphatic permeation should be kept in mind. If a careful routine follow-up can be assured, the " elective " block dissection in discontinuity may reasonably be avoided.

In the presence of enlarged and clinically metastatic lymphnodes remote from the primary growth, local wide excision of the primary growth and extensive lymphnode dissection in *discontinuity* should be undertaken, although arrest of the disease in such cases is exceptional. In some of

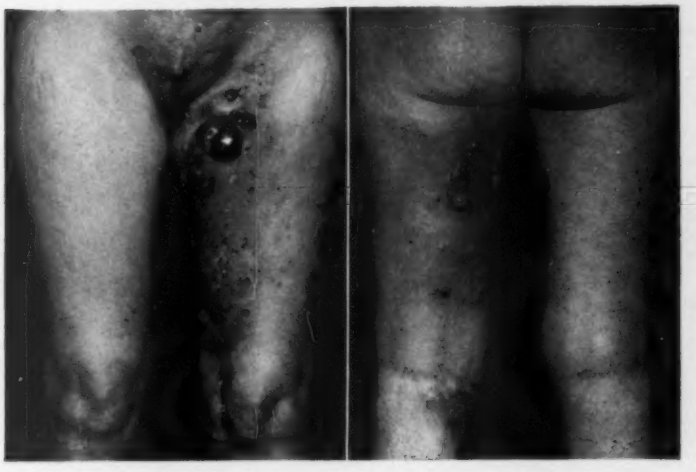


Fig. 15. Spread by lymphatic permeation from a malignant melanoma below the knee. The spread involves the anterior, medial and posterior aspects of the thigh. To illustrate the futility of the removal of a strip of skin from the site of the primary growth to the remote lymphnode. This practice should be universally condemned.

these patients ablation of the limb to include the regional lymphnode area is not only indicated and justifiable, but in fact the only method which offers a reasonably favourable prognosis. In such cases the ablation should be by forequarter or hindquarter amputation (Fig. 16). Disarticulation at the shoulder or hip for established lymphnode involvement should only be done when the lymphnodes are few in number, small, mobile and limited in extent.

It is difficult as yet to prove statistically if these measures are justified by the long-term survival, but there is little doubt that their rationale in selected cases is sound, whereas the removal of a three- or four-foot long, two-inch wide, strip of skin and clearance of the axillary or inguinal nodes has nothing to recommend it. Neither is it possible statistically to substantiate the policy of limb ablation as a routine, in view of the many

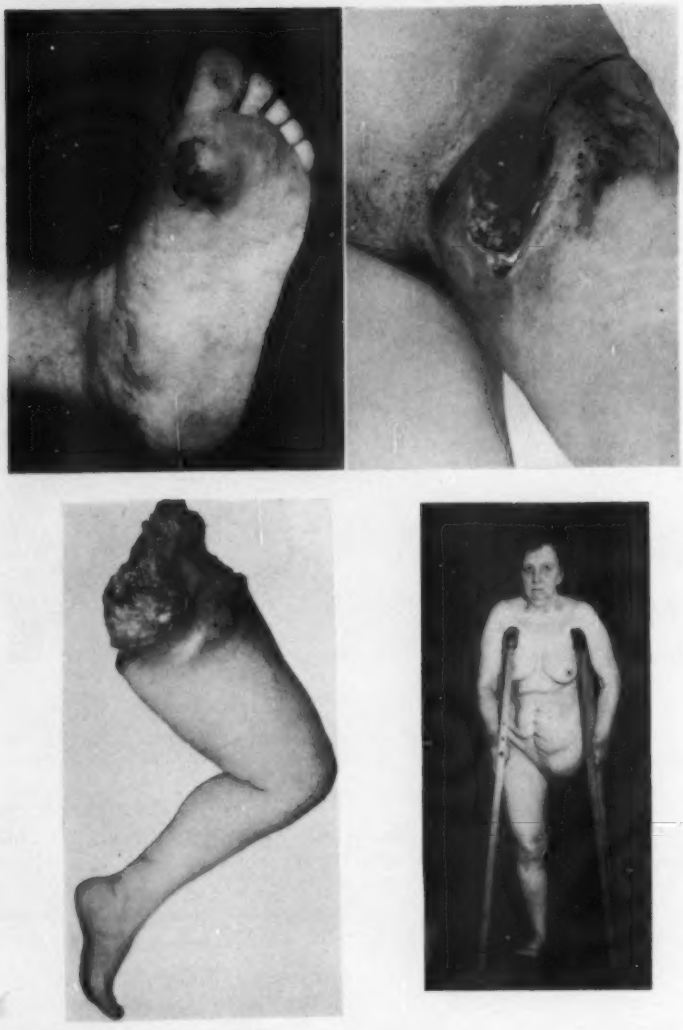


Fig. 16. The justification of a hindquarter operation. A. Primary malignant melanoma on the anterior part of the sole of foot excised in April 1955. B. Extensive, fungating black mass of metastatic lymphnodes, April 1958. C. Specimen of hindquarter amputation. D. Patient free from disease three years later.

variable factors and the small number of patients submitted to it. The improvement of results in the past ten years were due to the more adequate *initial* treatment and not to limb ablation, usually done as a last resort, and often too late.

The surgical treatment of malignant melanoma should therefore consist of: (1) wide local excision of the primary growth at the earliest possible moment; an adequate local excision requires a skin graft to close the defect; in most cases a linear scar indicates that excision was inadequate; (2) prophylactic block dissection of the regional lymphnodes, if this can be done in continuity with the excision of the primary lesion; (3) extensive block dissection in discontinuity for lymphnodes which become enlarged subsequent to a previous local excision of the primary growth; (4) limb ablation in carefully selected patients or as a palliative in the advanced case.

Radio-therapy

Although malignant melanoma is a radio-resistant tumour, radio-therapy has a place in its treatment. Radio-sensitivity and radio-resistance are relative terms and it is unfortunate that " radio-resistance " should have been accepted as synonymous with " unsuitability for radio-therapy " and that this should have influenced both surgeons and a majority of radio-therapists. Yet in 1939 Frank Ellis published his personal experience of 38 patients with malignant melanoma treated by radio-therapy, and one of his conclusions is worthy of repetition in full to-day, twenty-one years later: " This attribute (that melanomata are radio-resistant and unsuitable for radium therapy), moreover, seems to be so universally adopted at radium therapy centres in various parts of this country and in America, that it would seem the time is ripe for suggesting the contrary opinion, for which there can be adduced a good deal of evidence of an incontrovertible kind, that some melanomas, at any rate, are radio-sensitive."

Since then the efficiency of the radio-therapy apparatus has increased immeasurably; megavoltage in the form of radio-active Cobalt, 2 to 8 million volt X-ray machines and radio-active isotopes (such as tantalum wire or strontium foil) have been developed rapidly. The only armamentarium which does not seem to have improved with time is the flexibility of mind of some radio-therapists and of many surgeons. Yet besides Frank Ellis and myself, Margaret Tod, Ralston Patterson, Brian Windeyer, Miss Snelling have treated, and are treating, malignant melanoma radio-therapeutically.

It has never been a question of offering radio-therapy as an alternative to surgery, where surgery was indicated. The indications for radio-therapy, nevertheless, are quite definite: (1) prophylactically as a post-operative measure at the periphery of the excised area; (2) in the treatment of the irremovable growth; (3) when advanced age or site and extent of the

growth preclude adequate surgical removal; (4) as a palliative measure for recurrent nodules when other methods such as limb ablation, or excision, are inapplicable.

Chemotherapy

Techniques for the examination of living cancer cells in the circulating blood, and routine bone-marrow investigations, have revealed that dissemination may occur, and does occur, before there is any clinical evidence of dissemination. Warren Cole has demonstrated that ordinary clinical examination involving manipulation of tumours may be followed, sometimes instantly, by an increase in the detectable cancer cells in the peripheral blood. It has also been shown clinically that the intravenous and intra-arterial injections of various cytotoxic drugs can arrest this rising tide of circulating cancer cells.

The cytological identification of malignant melanoma cells is relatively easy, and to the skilled observer presents no difficulty; the ease with which tissue cultures of melanotic cancer cells can be kept alive and recorded photographically have placed in the hands of the clinician a very accurate method of studying the natural history of this tumour in phases which were not previously open to study.

Although chemotherapy of cancer is an ideal yet to be achieved, progress has been rapid both in the synthesis of a large number of new chemical substances, their screening and the clinical trial of some of them, and also in the technique of bringing these drugs to the site of the various lesions.

It is appropriate to emphasize that " there is still no chemical compound which alone is capable of producing a cure of cancer in man " (Farber, 1956), and Alexander Haddow (1959), the foremost authority on chemotherapeutic substances, stated: " I am fairly sure that the alkylating agents have no ultimate or permanent place in the chemotherapy of cancer ", but he adds, " on the other hand, one cannot be entirely sure."

Nevertheless, the most exciting event in the management of malignant melanoma is the chemotherapeutic attack on it. As already quoted earlier, Walter George Spencer concluded his Bradshaw Lecture on melanoma thirty-seven years ago with a sentence of prophetic quality, forecasting the chemotherapy of malignant melanoma.

Since then, specially in the past fifteen years, much progress has been made, new drugs have been put on prolonged clinical trial, new methods of administering these drugs have been developed, and new techniques are now being rapidly evolved. At this stage the intelligent use of chemotherapy requires a knowledge of the pharmacology of these drugs, their method of action, toxicity and relative efficiency, equally an intimate knowledge of the disease and above average specialized surgical skill.

This method, which has opened up entirely new fields of clinical research, is applicable, *par excellence*, to the treatment of malignant melanoma in all its stages, from the earliest till the very late disseminated final phase. This vast new field can be only summarized.

Malignant melanoma cells are vulnerable, and various drugs can produce profound alterations resulting in their death. The best known and most frequently used chemotherapeutic agent is Nitrogen Mustard and its derivatives, such as Leukeran, Degranol, Melphalan; all belonging to the group of alkylating agents. Less well explored as yet is the antimetabolite Metotrexate, and the antibiotic Actinomycin D.

For the past fifteen years, as and when each of these drugs became available, they were used as part of the treatment. Arrest or deceleration of rate of growth, shrinkage of lesions, and the disappearance of some of them, have been noted first with the derivatives R48, then CB1348 and later with Leukeran, and more recently with Melphalan. These substances, relatively little toxic in therapeutic doses, have been administered by mouth for prolonged periods of months or even years, and appeared to check the progress of lesions. Intravenous injections of Nitrogen Mustard proved more effective and for the past five years this, in the form of Degranol, was used as a routine before, during and after surgical operation for malignant melanoma. Encouragement led to the use of increased doses, from 50 mg. of Degranol given five times to a total of 250 mg.; the doses were raised to a total of 1,000 mg. a week in three divided doses. In a few selected patients almost certainly within a measurably short time from death from widespread visceral and skeletal metastasis, as well as vast numbers of cutaneous and subcutaneous lesions, massive doses, such as 3,000 mg., of Degranol were given in a week, following aspiration of the patient's bone-marrow and its replacement when the bone-marrow aplasia inevitably occurred (Westbury *et al.*, 1959). Unexpected and rapid regression of some of the visible deposits occurred. The method after a period of trial was discarded, as the bone-marrow aplasia could not be redressed by bone-marrow transfusion.

Creech (1958) and his colleagues reported the regression of malignant melanoma following limb perfusion with Nitrogen Mustard, and the use of extra-corporeal circulation preventing general bone-marrow damage.

Compact apparatus was devised at Westminster Hospital by Dr. Cliffe, embodying an oxygenator, the arterial and venous pumps and a thermostatic device. The use of a tourniquet, to prevent undue spill into the circulation, permits the perfusion of a limb with very large quantities of the selected drug. Regression of multiple lesions following this treatment has proved sufficiently encouraging to regard it, even at this early stage, as an alternative to the ablation of limbs by hindquarter or forequarter amputation (Figs. 12 and 15). In the few cases perfused so far by G. Westbury at Westminster Hospital, there has been no damage to the

circulation of the limb and no deleterious effect on the bone-marrow. Skilfully performed, such a perfusion inconveniences the patient but little, and necessitates a stay in hospital of about ten days.

Besides the use of Degranol intravenously as a chemotherapeutic cover before and after operation, and its use for limb perfusion, chemotherapy has been given as a prophylactic by mouth for six or more months following operation. At present Melphalan seems to be the most suitable drug in malignant melanoma. This substance, a phenyl alanine mustard, was synthesized in Professor A. Haddow's laboratories at the Chester Beatty Institute, and simultaneously in the Soviet Union under the name of Sarcolysin in 1959 (Larionov *et al.*, 1955; Blokhin *et al.*, 1958).

Larionov (1958) pointed out that the selectivity of anti-tumour action of various chemotherapeutic drugs is presumably due to the proper "carrier" of the alkylating group. In Sarcolysin (Melphalan) the essential amino-acid (phenylalanine) is the carrier of the alkylating (chlorethylamine) group. This may possibly explain the affinity of this compound for melanin-containing tumours.

Melphalan can be given pre-operatively, in 10 mg. doses orally daily, for five days preceding excision of a malignant melanoma, and it can be continued in the same dose for a further five days post-operatively. In smaller doses, 2 mg. daily, it can be given continuously for several months, with regular blood count control.

In patients with disseminated metastases, intravenous administration, if given very slowly, permits the administration of large doses, up to 160 mg. of Melphalan, given in divided doses of 40 mg. each over a period of 24 hours, and repeated at the end of seven to ten days. Regression of disease has been obtained in a few patients so treated. Leukopenia, a fall in the platelet count, can be controlled and bone-marrow aplasia guarded against, if the infusion is given slowly, 24 hours being required to inject 40 mg. of Melphalan.

Nevertheless, it seems necessary at this stage to guard against the risk of bone-marrow aplasia by aspiration of bone-marrow by multiple punctures of the innominate bones, sternum and lumbar vertebral spines (Humble and Newton, 1958), and the preservation of the marrow by freezing (Pegg and Trotman, 1959) for subsequent use, should this be indicated (Westbury *et al.*, 1959).

The place of chemotherapy in the treatment of malignant melanoma can thus be summarized: (1) as a pre- and post-operative measure, using Nitrogen Mustard intravenously or Melphalan orally; (2) as a maintenance treatment following excision, using Leukeran or Melphalan orally; (3) as regional perfusion of a limb using very large doses of Nitrogen Mustard or Melphalan in patients with advanced disease still localized to one limb (Fig. 15); (4) as a systemic treatment by slow infusion of Melphalan in the case of generalized metastatic dissemination (Fig. 12).

Prognosis

The prognosis of malignant melanoma is always uncertain and usually grave. The factors influencing prognosis have been critically analysed in a series of 226 patients seen and treated at Westminster Hospital in a period of 30 years. There were 100 male and 126 female patients. The age incidence is shown in Table I.

TABLE I

MALIGNANT MELANOMA

Age Incidence of 226 Patients

Age	0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90
No. of patients	3	7	53	43	47	39	17	14	3

This study deals with malignant melanomata arising in the skin, but includes ten patients in whom the primary lesion was in the mucous membrane at various sites: the mouth and palate, the nasal septum, the urethra and vulva, the anus, and one case of primary malignant melanoma of the tracheo-bronchial region. Intra-ocular lesions are not included. The incidence according to the anatomical site is shown in Table II, and includes four patients with metastases in whom no primary tumour could be detected.

TABLE II

MALIGNANT MELANOMA

Site Distribution in 226 Patients

Site	*Incidence*	*Percentage*
Lower Limb	105	46.4
Trunk	46	20.3
Head and Neck	38	16.9
Upper Limb	23	10.1
Miscellaneous	10	4.4
Unknown Primary	4	1.7

Prognosis depends in most cases on the size of the tumour; the larger the tumour the worse the prognosis. There are exceptions to this, when small and apparently insignificant lesions give rise to widespread metastasis; the stage of the disease when the patient seeks treatment is of great importance, and patients who present with satellite nodules, or palpable regional lymphnodes, are less likely to escape dissemination. The prognosis in women is definitely better than in men. Prolonged periods of survival, from five to ten or more years, are more often seen in women (White, 1959). It is well known that in children the clinical behaviour of a juvenile melanoma is that of a benign tumour, but recovery in true malignant melanoma in children, even in the presence of lymphnode invasion, is recorded. Of the three undoubted malignant melanomata in pre-pubertal patients in this series, two are alive and apparently free from disease for three years, and two years, respectively.

But the most important, in fact vital, factor in prognosis is the nature of the first or initial treatment. As pointed out earlier in this paper, Grey Turner, Margaret Tod, and others in the United States and in Sweden, deplored the treatment of malignant melanoma commonly carried out. In a review of 132 cases of malignant melanoma seen at Westminster Hospital (Cade, 1955–56), it was pointed out that the *patients who had received no previous treatment of any kind had a 50 per cent. chance of control of the primary growth, whereas those who had any form of " inadequate " treatment—in fact, the majority of patients—fared much worse, 73 per cent. developing local recurrence.*

The deplorably poor management of malignant melanoma needs emphasizing, and the 226 patients were subdivided into three groups: (1) those who had received no previous treatment when first seen; (2) those who had received " adequate " treatment to the primary growth, and were referred for post-operative management or for treatment of metastases without local recurrence; (3) those who had received " inadequate " treatment before being seen at Westminster Hospital. The terms " adequate " and " inadequate " are defined as follows: " adequate " treatment consisted in wide excision, in most cases necessitating a skin graft, and in whom there was no local recurrence. " Inadequate " treatment included under the general heading of " tinkering ", cautery, electrolysis, diathermy, " some " X-ray therapy (generally given *not* by a trained radio-therapist, usually with vague details as to physical data or dose); biopsy of part of the lesion with subsequent delay of two or more weeks; excision with closure without graft in lesions larger than 2 cm. in diameter (Figs. 13, 14 and 17). In 112 patients critically assessed (Cade, 1955–56) on the basis of the original or initial treatment, the results were classified as " good " if there was no local recurrence, and " bad " when local recurrence developed at the site previously treated. This assessment is shown in Table III, and indicates the importance of the initial treatment as regards prognosis.

TABLE III

RESULTS ACCORDING TO PREVIOUS TREATMENT

(112 *patients*)

Previous Treatment	*Results of Definitive Treatment*	
	Good	*Bad*
None	13 (50%)	14 (50%)
Adequate	11 (42%)	15 (58%)
Inadequate	16 (27%)	43 (73%)

It should be noted that the subdivision into " good " and " bad " results in Table III refer to the local control of the lesion only and not to the ultimate five-year survival or to lymphnode or blood-borne dissemination. It indicates only the possibility of controlling the primary growth according to the adequacy of the initial treatment. But the initial treatment profoundly influences the prognosis. Most patients in whom the initial

treatment was inadequate are in fact beyond help. Preston *et al.* (1954) found in their series of 225 patients, that when the initial treatment failed to control the primary lesion, the five-year survival rate was one patient among 58, or only 2 per cent. The largest single anatomical site, the lower limb, consists in this series of 105 patients; of these 61 patients can be assessed for five or more years, and the correlation between adequacy or inadequacy of treatment with the ultimate prognosis in this group is shown in Table IV.

TABLE IV

MALIGNANT MELANOMA

Lower Limb: 61 *Patients*

Five years or more survival

First treatment	*Total*	*Alive*	*Percentage*
Adequate	29	16 (19)	50% (65%)
Inadequate	32	5 (7)	15% (21.8%)

(The figures in brackets indicate the number of patients alive, including those with disease; the figures not in brackets refer to patients free from disease.)

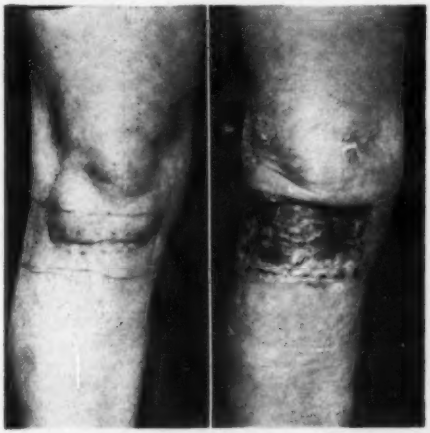


Fig. 17. The "rescue operation". A. Scar of a recent inadequate excision; linear scar, no skin graft. The likelihood of a local recurrence is very great. B. Re-excision and skin graft.

Table IV indicates that whereas of a total of 29 patients adequately treated, 65 per cent. were alive for five or more years and of these 50 per cent. were free from disease, when the initial treatment was inadequate, of a total of 32 patients only seven were alive for five or more years, and of these only five were free from disease. The mortality of those inadequately treated was, therefore, 72 per cent., whereas the mortality of adequately treated patients was 27 per cent.

This obvious correlation between the first treatment and the ultimate results reflects the disquieting situation, that the initial treatment of malignant melanoma leaves a great deal to be desired.

Results

Of the 226 patients, 145 are assessable for five years and more, and Table V indicates a survival of 40 per cent., of which 24.8 per cent. are disease free. The figures also show that the prognosis is better in women than in men. In malignant melanoma, five years survival is of less significance than in other tumours, as recurrences and dissemination occur in the sixth to tenth year, continue to occur and survival at ten years falls to 22.4 per cent., of which only 14.2 per cent. are disease free.

TABLE V

MALIGNANT MELANOMA

Five Years or more Survival

Total number of patients	145			M.: 64 F.: 81	
Number of patients alive	58	=	40%		
Disease free ..	36	=	24.8%	M.: 12 F.: 24	

Ten year survival: 49 *patients*

Alive	11	=	22.4%
Disease free ..	7	=	14.2%

The survival at five and more years, according to the site of the primary growth and the sex of the patient, is shown in Table VI.

TABLE VI

MALIGNANT MELANOMA

Five Years or more Survival

			M.	F.
Lower limb	68	patients	19	49
Disease free	22	,,	5	17
Head and neck	28	,,	21	7
Disease free	9	,,	6	3
Trunk	24	,,	16	8
Disease free	2	,,	0	2
Upper limb	16	,,	5	11
Disease free	3	,,	1	2
Miscellaneous and Unknown Primary	9	,,	3	6
Disease free	0	,,	0	0

SUMMARY AND CONCLUSIONS

Malignant melanoma is not naturally as deadly as other more common cancers: the lung, the oesophagus, the stomach.

The five- and ten-year survival figures compare favourably with other neoplasms, providing the treatment is adequate.

The importance of the first or initial treatment is paramount, and the disastrous effect of inadequate treatment is emphasized.

To the student of to-day and the doctor of to-morrow, with whom rests the fate of the patients of the future, I would recommend the following ten rules as a guide to the management of malignant melanoma, in the hope that the present disquieting state might be remedied: (1) Moles are blemishes—not " beauty spots ". (2) Scars are safer than moles. (3) Remove juvenile melanoma before puberty. (4) Do not " tinker " with pigmented lesions. (5) Do not " scratch " in the lymph fields. (6) Do not " throw " away the specimen. (7) Remove the primary growth widely *tri-dimensionally*. (8) Look critically at 1960 editions of surgical textbooks—containing 1930 information. (9) Do not deny the patient radio-therapy. (10) Practise chemotherapy.

Although it is the lot of man but once to die, the victim of malignant melanoma need not die by inches from the black death. The measures science gives us in abundance are to be used not timidly but bravely to combat this pigmented foe, who claims the fairest and the youngest and the old with equal impartiality.

I am indebted to many colleagues for their help in various ways in the management of the patients, whose clinical fate is the basis of this lecture. In particular I wish to express my thanks to Miss P. Wheatley, M.B.E., Superintendent Radiographer at Westminster Hospital, for the exemplary and painstaking care of the notes and the follow-up of patients; to Dr. Peter Hansell for the photographic records; to Mr. Redman, of the photographic unit of the Royal College of Surgeons, for preparation of the slides, and above all to the patients, whose courage in the face of adversity permitted me to continue one form of treatment after another till no more could be done for them.

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THE WOLFSON FOUNDATION

THE PRESIDENT OF the Royal College of Surgeons of England, Sir Arthur Porritt, acknowledges with utmost gratitude on behalf of the College Council a grant of £250,000 from the Wolfson Foundation. In making this grant, the Trustees of the Foundation recognize the invaluable work of the College in this country and in the Commonwealth overseas.

The gift will be applied primarily to the provision, furnishing and equipment of the Hunterian Museum. This Museum—now being rebuilt following its destruction by bombing—is expected to be finished by the spring of 1962, and is to house the famous collection of anatomical and pathological specimens collected by John Hunter, and purchased by the Government of the day after his death in 1793. The Museum is the " heart " of the College, the centre of its historic tradition and the inspiration of its scientific thought. It was the expressed wish of the Trustees of the Wolfson Foundation " to assist in maintaining its position as probably the finest of its kind in the world ".

THE INFLUENCE OF TECHNICAL ADVANCES ON MEDICAL PRACTICE: THE ELECTRON MICROSCOPE

The Thirteenth Alex Simpson-Smith Memorial Lecture delivered at the West London Hospital Medical School

on

11th July 1960

by

Gilbert W. Causey, F.R.C.S.

Professor of Anatomy, Royal College of Surgeons of England

ALEXANDER SIMPSON-SMITH, to whose memory this lecture is dedicated, was born just 60 years ago, on 2nd June 1900, and, after a brilliant academic career, made rapid progress in the surgical world until he was sacrificed in his prime in 1942 to the horrors of war.

The majority of the lectures given in his memory have been devoted to subjects of direct surgical interest; the details, however, of Simpson-Smith's career, borne out by those who knew him, show that he was one of those, very precious to us, who combine the dexterity and clinical acumen of the successful surgeon with the thoughtful and forward-looking outlook of the research worker. Throughout his life there run the parallel activities of the practising surgeon and the more academic work which we associate with the time he spent as Richardson Research Scholar at the Mayo Clinic and the Massachusetts General Hospital, as an Anatomy Demonstrator, and his long association with the Buckston Browne Farm of the Royal College of Surgeons, where he worked from 1934 to 1939, as the Research Fellow of the Association of Surgeons. These all indicate the searching mind combined with the active practice of the relief of pain and suffering.

And so to-day, as a tribute to this man, I feel that I may be forgiven for emphasizing the laboratory side of his work, and acknowledging this by discussing one of the modern impacts of the development of physical instruments in relationship to the advances in medicine.

There are two possible distinctions that can be made between the direct application of physical instruments to diagnosis and the application of physics to biological research. A very typical example of the first is the thermometer. Galileo (1564–1642) was the first to make a useful thermometer, by including air in a glass vessel and inverting it over a dish of water. He showed in this way that variations in temperature of the bulb gave rise to variations in the height of the water in the tube. The errors of this mechanism are clear to us now, the most serious being the presence of water vapour in the air; but Galileo's thermometer was used, nevertheless, by Sanctorius (1561–1636) for measuring the temperature of the body.

The thermometer was improved by Boyle, the physicist, and, after the middle of the 17th century, became an instrument of common use; to-day we tend to forget that the clinical thermometer is the result of physicists

observing the alterations in volume of air, mercury or other substances with temperature. This example can be multiplied over and over, so that, as Lord Cohen, lecturing recently at Glasgow, said, ". . . to-day practically every new instrument of precision which is elaborated for the use of the physicist, the chemist or the engineer finds its niche in the resources of the scientific physician". But the discoveries and the efforts of the physicist and the chemist are applied more directly to the interpretation of biological phenomena, which, perhaps rather invidiously, go under the general term of fundamental research. Just one recent example of this: the oscilloscope was developed by the physicists in the early twenties of the century, and since its application by Erlanger and Gasser in 1926 to the recording of the electrical changes in nerve it has become one of the most ubiquitous and popular instruments in all forms of research in human biology. Now, indeed, instead of using it solely as a research tool at the marginal limit, it is present everywhere, in the undergraduate laboratories for teaching purposes, in the research schools, in the wards, modified either in the electrocardiogram or the electroencephalograph; our operating theatres have now become surrounded by batteries of oscilloscopes to record every action and activity of the human body as it goes through the hazards of the brilliant operations performed to-day, to which this type of control mechanism is an essential adjunct.

The microscope was probably invented by Janssen in about 1590. It was a natural development of the use of lenses, which had come into use just before that time to make telescopes. This again was essentially a physicist's discovery. The images were distorted and colour fringes were always present, but a mere 50 years later they were sufficiently perfected for biological work. Malpighi of Bologna, for example, examined in 1661 a lung, the arteries and veins in it, and also many other organs of the animal body. Leeuwenhoek used simple microscopes to examine the capillary circulation, muscle fibres, blood corpuscles, bacteria, spermatozoa and hundreds of other forms of animal and plant tissues. The physicists' instrument was launched into biological studies.

The developments of the optical microscope do not concern us here, except that we should note that, during the 200 years from 1650 to 1850, the microscope was developed into a compound instrument with compensations for the chromatic and spherical aberrations, so that by the middle of the 19th century magnificent instruments were in use throughout the world. Histological investigation with the optical microscope certainly held the attention of some of the foremost minds in biological research, Schwann, Ranvier, Cajal in the world of the nervous system or Kolliker, Kuhne, Virchow and the morbid anatomists. It may have been surpassed in quantity since then, but probably not in quality.

This stage in the development of the optical microscope leads us to a critical point. It is not even theoretically possible to increase the resolution obtained by an optical system beyond a certain limit, which is determined

by the wave-length of the light that is used to illuminate the optical system. More exactly, this means that it is possible with ordinary white light to resolve two particles about half the wave-length of light apart, and taking the wavelength of white light as 5,000 Å, or ten-millionths of a millimetre, a resolving power of about 1/5 micron is possible. With ultraviolet light of shorter wave-lengths of about 2,000 Å, better resolving power was theoretically possible, and in fact these limits of resolution were practically obtained. It looked, therefore, as though a limit to the available resolving power of microscopes had been reached by the end of the 19th century. But during the last ten years of the 19th century, other epoch-making events were taking place in physics laboratories, entirely unrelated at the time to microscopy, but later to have an immense effect on that subject. Crookes, Roentgen, Rutherford and very many others in the field of physics were busy with the waves and particles produced, not only by a Crookes tube, that is the radiation from a hot cathode in a vacuum, but also with the products of disintegration of uranium and radium. It is extremely interesting to see that here in the electron beam produced by a cathode ray tube we have a wave-form, whose length is as little as a thousandth of that of ultraviolet light; the obvious possibilities were not slow to be seen. The microscope, optically illuminated, had reached the limit of its resolving power. Here was a wave form whose wave-length was a minute fraction of that of visible light. Could anything be done about it? Again it must be emphasized that the possibilities of the development were worked out before the actual practical applications were made.

In 1926 Busch published a paper showing that theoretically the mathematical computations indicated that an electromagnetic field would act upon an electron beam in almost exactly the same way as a glass lens does on visible light. With these fundamental concepts firmly established, it was not long before Ruska and Ruska working in the Siemens laboratories produced an electron microscope. This means that a machine has now been perfected, almost identical in principle with the light microscope, in which the light source is replaced by a hot cathode, using a voltage of anything from 50–100 thousand volts; the stream of electrons emitted from it is passed through a series of electromagnetic lenses on exactly the same principle as the sub-stage condenser, the objective and the eye-piece of an optical microscope. The beam of electrons passes through the specimen to be examined and the scatter of the electrons produces an image which can be focussed on a photographic plate or fluorescent screen placed at the end of the magnifying system.

The advance that electron microscopy has made is one of resolving power. The theoretical resolution is no longer tied down by the comparatively long waves of visible light, but by other physical phenomena associated with the use of very small particles or waves; instead of being able to get the resolution of about half the wave-length of the electron beam, the best resolution that has been obtained is somewhere in the region of five,

possibly three, Ångströms. This has opened up an immense new world from the resolving power of 2,000 or more Ångströms possible in the light microscope.

The details of construction of the elaborate, expensive instruments of to-day do not concern us, but with suitable lenses, with a sufficiently high vacuum and thin enough sections of suitable material, it is possible to get a resolution of fine detail of human and animal tissues, such as has not been achieved before. For the last ten years hundreds of workers throughout the world have concentrated on the development of these techniques until now there are some thousands of microscopes of this type in use throughout the world, and the number is increasing almost daily.

Before going on to discuss and illustrate some of the results of the use of this technique, and showing its application to medicine, I must emphasize two of the major draw-backs to the electron microscope. First, there is no evidence at the moment that we shall be able to examine living tissues in a machine of this type, though attempts are at present being made. Secondly, we lose the value and effect of staining methods, which have been developed by the optical microscopists for distinguishing different tissues. But the important developments in histo- and cyto-chemistry that have been made in the last 50 years should become more directly applicable at the electron microscopic level, particularly with regard to the possible removal of specific chemical substances from the cell by enzymes. Staining of this sort is at present in its infancy in electron microscopic techniques, but the use of enzymes and heavy metals is being actively investigated, and I have no doubt that whereas 200 years were taken to develop the optimum of the light microscope a mere 20, 30, perhaps 50, will be needed for the same development to take place in the electron microscope.

As with so many other technical advances, there is a considerable addition to the terms which we use. An illustration of this is the electron micrograph of the epithelium of the prostate gland (Fig. 1). Here the correlation with the well-known histological picture can be seen. The cells are outlined and the membrane surfaces between the individual cells, made more distinct here by the deposition of the heavy metal, osmium, with which the specimen was fixed, are outlined here. The nucleus is electron dense, and the structures within it are not clearly distinguishable. On the border of the cell tiny villous projections towards the lumen can be seen, a very common finding in all cells adjacent to ducts, when examined in the electron microscope. They must be clearly distinguished from cilia, whose structure has been so well described by a number of workers and reviewed recently by Fawcett. Each cilium has nine filaments peripheraiiy placed and one pair placed centrally, all of which are related to a centriole in the cytoplasm. In the cytoplasm itself the endoplasmic reticulum is a new term introduced by Palade; it has also been called the alpha-cyto membranes by Sjostrand. In this type of cytoplasmic structure we have well marked channels, sometimes with small granules on their surfaces

and sometimes agranular; the variations in this endoplasmic reticulum under different conditions form one of the important fields in which work is going forward. There are mitochondria here, the presence of which was known to the optical histologist, but their internal structure and clear identification has been the work of the electron microscopists during the last ten years. Granules, vesicles, and the vesicular aggregate of the Golgi apparatus are all structures within the cytoplasm that have become subjects of close investigation with the resolution of this instrument.

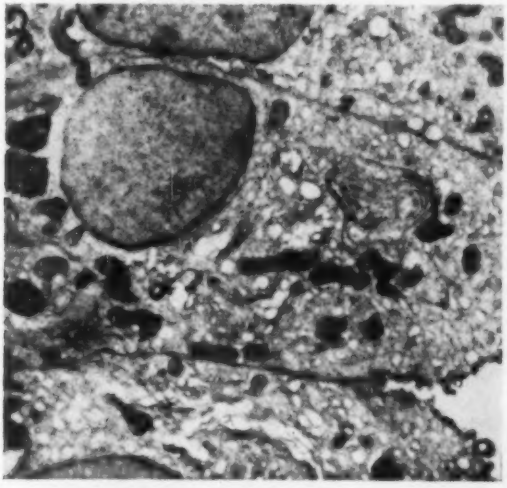

Fig. 1. Electron micrograph of three cells and the basement membrane from the epithelium of the mouse prostate, illustrating the various cellular occlusions. (×8,000.)

There are many of the tissues and structures in the body that have been examined, in which great progress has been made in the clarification of their structure, but time will only allow a cursory glance at one or two of these subjects. The structure of muscle fibres has been brought to a level of macromolecules. The rods and cones of the retina have been analysed in considerable detail, and work on the kidney has proceeded so far that it is now of some obvious practical value to examine human kidney biopsy material in the electron microscope, in the diagnosis of nephrotic conditions.

One of the most important contributions in structure revealed by the electron microscope has been the demonstration of the relationship between nerve fibres and Schwann cells, where the fibres are invaginated

into the cytoplasm of the Schwann cell and connected to its surface by a mesaxon (Fig. 2). The relationship of this mesaxon to the myelin lamellae of the medullated nerve fibre has been closely examined by Robertson, Fernandez-Moran, Finean and many others. The relationships shown here between the biochemical structure of the myelin, the electron micrograph of the distribution of the laminae within the myelin, and the X-ray defraction pictures have formed an exciting part of biological advance.

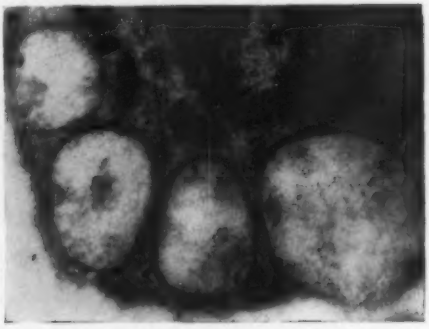

Fig. 2. Electron micrograph of non-myelinated nerve fibres, showing the invagination of the nerve fibres into the Schwann cell cytoplasm. (×50,000.)

After indicating some of the normal tissues as they appear in the electron microscope, I will now try to show some of the lines of experimental and pathological approach. I would first wish to acknowledge the help of my colleagues Dr. Barton, Dr. Hoffman, Dr. Stratmann and Mr. Edwards in the work that will be used to illustrate these lines from the Department of Anatomy at the Royal College of Surgeons. The application of the physical principle has been indicated, the development of the machine and its techniques outlined. Then comes the application of the techniques to normal tissues leading finally (from the point of view that is being emphasized to-day) to the investigation of abnormal tissues and the application of the technique of medicine.

In neoplasms there are structural differences between malignant cells and their normal precursors. We have been interested in the normal Schwann cell, and I would draw your attention to one feature only, the relatively regular surface of the nucleus. In the envelope of the nucleus two electron dense lines can be distinguished in this type of material, one related to the cytoplasmic side and the other to the nuclear side. In our examination of tumours of Schwann cells, produced by the carcinogen dimethyl-benzanthracene, one of the features which has impressed itself on our minds is the apparent change in the nuclear surface. This has

not, of course, happened in all the cells, but it seems to us that with activation, increasing towards the loss of control that is apparent in malignant disease, a larger number of the cells show irregular overall configuration of the nucleus and, in particular, a loss of the almost parallel distribution

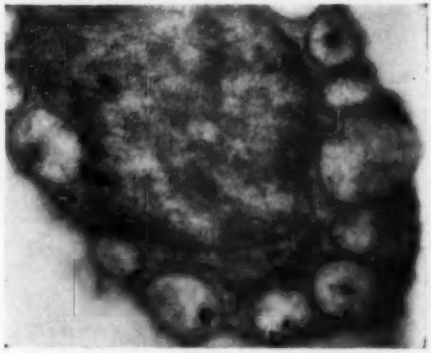

Fig. 3

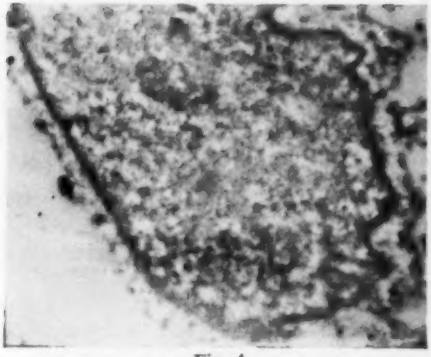

Fig. 4

Figs. 3 and 4. Electron micrographs of the nuclear surface of normal and neoplastic Schwann cells. (×20,000.)

of the two laminae of the nuclear envelope. This is illustrated in Figures 3 and 4. The picture of the malignant nucleus shows the sort of irregularities and protuberances which are so common in these nuclei. These are seen in normal inactive cells and I am among the many who believe that the mitochondria are related, probably causally, to the nuclear envelope. We would suggest that the replacement of the mitochondria probably takes place at the nuclear cytoplasmic surface. This may not be by any means exclusive, and does not deny the possibility of the division of the

formed mitochondria within the cytoplasm, but gives us two modes for the production of these important metabolic organelles. This would suggest that under extreme stress the cell produces new mitochondria, from the nuclear surface, whether the stimulus is an embryological development or a malignant change and that probably the actual division of the mitochondria is a second mechanism which may be brought into play at the same time or a more normal method of maintaining the mitochondrial number and distribution in which might be called physiologically, as opposed to pathologically, active cells.

This is only one site within the cell at which one would look for structural changes. The most exciting work, in my opinion, has come in the last few months from the electron microscopists of the Rockefeller Institute. The cytoplasm of the liver cells has been examined very systematically in the early stages of the artificial production of tumours of liver cells, and

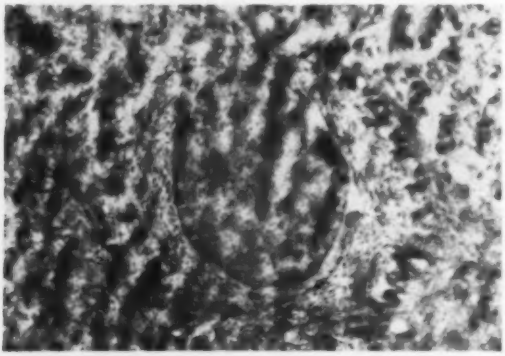

Fig. 5. Electron micrograph from the prickle cell layer of human skin, showing fibrillary cytoplasm and desmasomes. (×6,000.)

the early changes in both the ribonucleic acid granules and in the mitochrondria have been tracked with most patient and meticulous care in the early stages of these changes. From the same Institute came the study by Palade of the life history of the zymogen granules in the pancreatic glandular cells.

Leaving neoplasms for a moment, let us look at the skin.

The ultrastructure of the basal cells and their relationship to melanin formation, as well as the transitions from these basal cells to the spinous cells, the stratum lucidum and the cornified layer, show the tonofibrils and the attachments of the cells to each other with great clarity. The formation of keratohyalin granules in the surface cells, where the transition is seen with loss of cellular outline, nuclear definition and increase in opaque granules, accompanying loss of tonofibrils or fibrillary elements in the cytoplasm, stresses a gradual change in these cells; it also amplifies the

older knowledge of the gradual formation of less and less live cells, as we come towards the cornified layer which is shed. Someone has calculated that we shed 40 lb. of these keratinized cells from our skin during a lifetime.

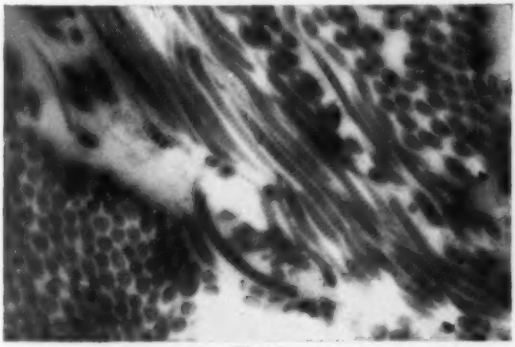

Fig. 6

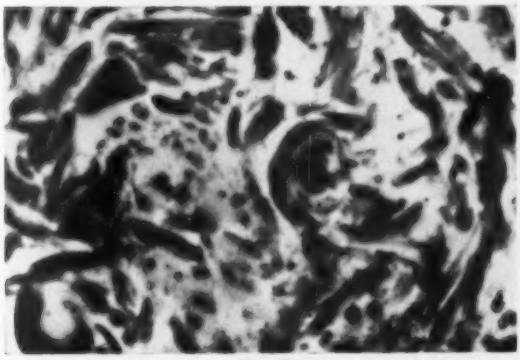

Fig. 7

Figs. 6 and 7. Electron micrographs of a normal collagen fibre (6), showing the typical banding, and of elastic fibres (7) from a case of pseudoxanthoma elasticum. (×10,000.)

The effect of viruses on these cells has been very beautifully demonstrated by Dourmashkin and Bernhard. The whole cytoplasm is disrupted, the nucleus pushed to one side and the tiny vesicular virus particles are diffused throughout the whole of the cytoplasm of affected cells.

Equally interesting is the dermis. The work on collagen fibres and their relationship to reticulin and elastin is one of the most fascinating sides of electron microscopic work (Figs. 6 and 7). The clear definition of the banding of collagen fibres and their identification on this criterion does not

necessarily tally with the biochemical classification of collagen, resolved by the proline estimations or of digestion with enzymes such as elastase or collagenase. But many people are busy elucidating these relationships and we should soon have favourable results. This is certainly a problem of the greatest immediacy and importance. The changes in the size, banding, the period of collagen, and their relationship to the production of elastin and the changes in this elastic tissue both with age and disease, underline most strikingly the change in outlook that has occurred in the last years; formerly we looked upon fascia as a binding tissue, inert from a functional point of view, with the result that this sort of tissue has been relegated too long to the background. But now the changes in rheumatism and fibrositis, with their enormous wastage of man-hours, surely require the most vigorous attack by this and other methods. The extreme

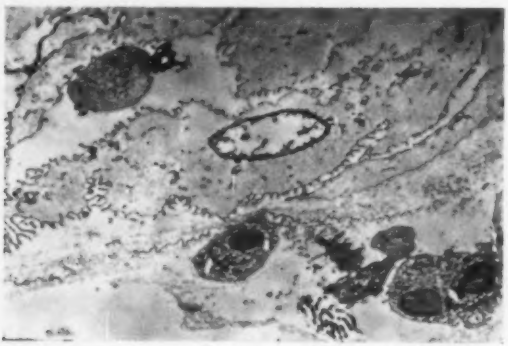

Fig. 8. Sections of typical cells in a low-power electron micrograph taken from the stomach by gastric lavage. (×5,000.)

alteration of the collagen structure of the dermis can be illustrated by the accompanying photograph of elastic tissue from a case of pseudoxanthoma elasticum (the specimen was kindly supplied to me by Mr. Harold Edwards). Large masses of irregular, blunt-ended elastic fibres, such as are illustrated, are found in the dermis in this condition, with the loss of the regular transverse banding of the collagen fibres.

Electron microscopy, besides being used in kidney biopsies, has also been adopted for human patients after removal of specimens of both colonic and gastric mucous membranes with a small punch; but there is another method of approach which we have used in the human patient, to look at the electron microscopic picture of desquamated cells, to see whether such an attack would shed any light or give us any clue as to the state of the organ. We have been particularly interested in the stomach and, through the courtesy of Mr. Burge, we have been able to examine the cells recovered from gastric washings. These can be fixed and spun down;

as long as they are kept chilled, they retain a considerable amount of their internal structure, including the distinctive nucleus and the outline of the nucleus. If the increasing activity of cells were related to a statistical distribution of increased nuclear irregularity, we have a useful method of investigating the condition of the stomach wall by the simple procedure of washing out the stomach. Figure 8 shows sections of these cells, obtained in this way. There are two points of especial interest. First, are there variations in the nuclear configuration? Second, what is the probable site of origin of the cells at which we are looking? Table I shows the distribu-

TABLE I

THE DISTRIBUTION OF REGULAR AND IRREGULAR NUCLEI FROM GASTRIC WASHINGS IN 15 PATIENTS

Case No.		*Mucosal Cells*	*"Normal" Nuclei*	*"Abnormal" Nuclei*
1		50	18	1
3		50	22	0
5	No	50	16	1
8	stomach	50	8	1
9	lesion	50	13	0
11		50	11	2
4		50	10	9
7		50	17	9
12	Gastric	50	8	5
13	carcinoma	50	3	13
15		50	8	10
10		50	6	10
16	Benign	50	4	9
17	ulcer	50	1	16
26		50	3	11

tion of regular and irregular nuclei from specimens obtained by gastric washing in 15 patients; there is a clear distinction between the pathological stomachs and the normal ones, classified on their radiological and operative findings. One would like to correlate this change with some change in the stomach wall, but I have included two pictures, neither are very good in themselves, but both are important from the point of view of this application of electron microscopy to diagnosis. The first one (Fig. 9) shows a piece of the gastric surface of the human stomach in which the cells are being drawn away and shed; they are typified by cellular bridges and a rather elongated outline. The second (Fig. 10) shows cells scraped from a human oral pharynx, put through the same fixation and embedding treatment as the stomach washings. It seems probable that the cells in the gastric washing can come either from the stomach surface or from the upper digestive passages, possibly swallowed before the stomach washout or removed by the contact of the stomach tube.

These figures and results are stimulating. They lead us in the field of electron microscopy towards its future for medical men, and give us a keen sense of the importance which this one technique which I have dealt with

in some detail to-day may have, and in my opinion should have, on the future relationship with medical diagnosis. The control of the chemical treatment of cancer by study of the configuration of cancer cells will be one of the possible results which these may have on treatment. There are many other fields, but I think that the opportunity that has been given to me

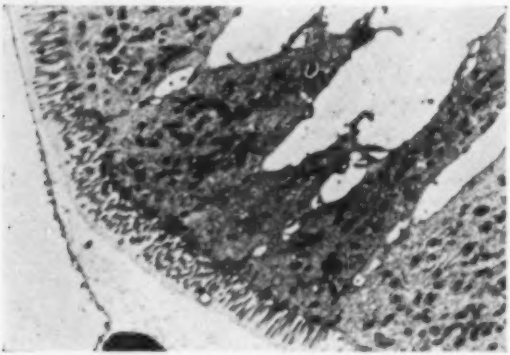

Fig. 9. Desquamating cells from the surface epithelium of the human stomach. (×9,000.)

to-day, of indicating some of the advances in a field where the developments of the last 10 years have been so enormous, must impress on us all the great contribution which men of the mental calibre of Simpson-Smith make to medicine. They keep their minds open, not only to the work in hand,

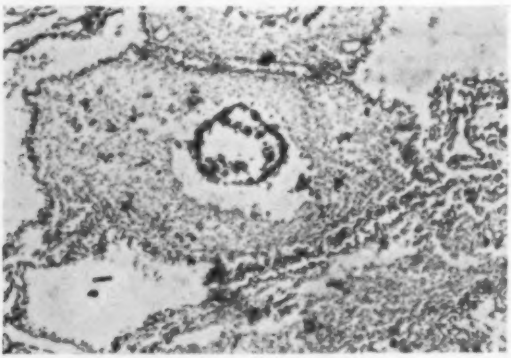

Fig. 10. Electron micrograph of a thin section of cells from the buccal mucous membrane. (×8,000.)

but to the correlation between past findings, present work and future possibilities. They surely are the seekers in Medicine, the seekers so well described by Eddington: "How easy in a popular lecture to tell of the findings, the new discoveries which will be amended, contradicted, superseded, in the next fifty years. How difficult to convey the scientific spirit of seeking which fulfils itself in this tortuous course of progress towards truth! You will understand the true spirit neither of science nor religion unless seeking is placed in the forefront."

COLLEGE PUBLICATIONS

READERS ARE REMINDED that the following publications issued or sponsored by the College may be obtained from the Editorial Secretary, Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2.

A Catalogue of the Portraits and other Paintings, Drawings and Sculpture in the College. By William Le Fanu, Librarian. 184 pages with 4 coloured and 52 black and white plates. £1 10s. 0d. (postage 1s. 9d.).

The History of the College. By Sir Zachary Cope, F.R.C.S. 376 pages, fully illustrated. £3 3s. 0d. (plus 2s. postage).

Lives of the Fellows, 1930–1951. By the late Sir D'Arcy Power, K.B.E., F.R.C.S., Honorary Librarian, and continued by W. R. Le Fanu, M.A., Librarian. A single volume, bound in blue cloth, of 889 pages, containing the Lives of all Fellows known to have died between 1930 and 1951. £2 2s. 0d. post free.

A Record of the Years from 1901 *to* 1950. Edited by Sir Ernest Finch, M.D., M.S., F.R.C.S. A slim volume, illustrated, containing a brief history of the College between the centenary and the 150th anniversary of the foundation with lives of all the Presidents since 1900, written by special contributors from their personal knowledge. In red cloth 9s. post free or red paper covers 5s. 6d. post free.

A Guide to the Hunterian Museum (*Physiological Series*). This gives a brief account of the physiological section of John Hunter's museum, the scope, design and historical value of which is unique. 48 pp. 1s.

A Descriptive and Historical Catalogue of the Darwin Memorial at Down House. Charles Darwin and his family lived at Down House, near Orpington, Kent, for forty-two years and it was here that most of his scientific investigations were made, including his work on the Origin of Species, published in 1859. 33 pp. 1s.

The Portraiture of William Harvey. The Thomas Vicary Lecture for 1948 by Sir Geoffrey Keynes, M.A., M.D., F.R.C.S. With a descriptive catalogue and 33 reproductions of the portraits. £1 5s. 0d.

**William Clift.* By Jessie Dobson, B.A., M.Sc., Anatomy Curator. A biography, fully illustrated, of the first Conservator of the Museum at the College. Published by William Heinemann Medical Books Ltd. Bound in blue cloth; 144 pages with frontispiece portrait and 31 plates. 8s. 6d. post free.

The present position of cardiac surgery. The Bradshaw Lecture for 1957 by Sir Russell Brock, M.S., F.R.C.S. Blue cloth binding, 6s. 0d. post free.

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* A separate cheque for this publication would be appreciated.

PRESENTATION OF AN HONORARY FELLOWSHIP OF THE ROYAL AUSTRALASIAN COLLEGE OF SURGEONS TO THE PRESIDENT OF THE ROYAL COLLEGE OF SURGEONS OF ENGLAND

ON 20TH FEBRUARY 1961 the President of the Royal College of Surgeons of England was admitted to Honorary Fellowship of the Royal Australasian College of Surgeons by its President, Mr. Leonard Lindon.

Mr. Lindon holding the two prints presented by the Royal College of Surgeons of England, and Sir Arthur Porritt holding his Diploma of Honorary Fellowship of the Royal Australasian College of Surgeons.

The citation was given by the Senior Vice-President of the Royal Australasian College of Surgeons, Professor Neville Sutton, who spoke thus:

" Mr. President,

" I have the honour and great pleasure to present to you for admission as an Honorary Fellow of the Royal Australasian College of Surgeons, Sir Arthur Espie Porritt, Knight Commander of the Most Distinguished Order of St. Michael and St. George, Knight Commander of the Royal Victorian Order, Commander of the Most Excellent Order of the British Empire, President of the Royal College of Surgeons of England and Immediate Past President of the British Medical Association, Surgeon to St. Mary's Hospital, London.

" On an occasion such as this it is indeed a matter of great satisfaction to remember that our college is an Australasian College in which the best of surgery in the two sister

nations of the South Pacific, the Commonwealth of Australia and the Dominion of New Zealand, is so successfully united.

" For Sir Arthur was born at Wanganui in New Zealand, son of a medical father, who was himself an English Fellow. After attending school there he commenced his medical education at the University of Otago in Dunedin.

" After a few years he showed those qualities of academic attainment, fondness for and success in outdoor sport, manhood, truth, courage and moral force of character which were specifically enumerated by Sir Cecil Rhodes as the attributes to be sought in men he wished to benefit by an extended period of education at the University of Oxford.

" Sir Arthur was chosen as a New Zealand Rhodes Scholar for 1923 and proceeded to Magdalen College, where he graduated first in Arts and later he graduated in Medicine. His Clinical School was St. Mary's Hospital, London, and he gained his Fellowship of the Royal College of Surgeons of England in 1930.

The President of the Royal College of Surgeons of England, Sir Arthur Porritt, receiving his Diploma of Honorary Fellowship from the President of the Royal Australasian College of Surgeons, Mr. Leonard Lindon. In the background is Professor Neville Sutton.

" His surgical life has been centred at St. Mary's, where he was appointed first a Junior and later a Senior Surgeon. Since those days he has been known to a long succession of medical students, young graduates and junior surgeons as a most persuasive and successful teacher of surgery—a career of teaching which reached a high point with the publication of the *Essentials of Modern Surgery* in 1938. This was edited and largely contributed to by himself and his co-editor, Handfield Jones, and this student's textbook set a new standard for such works which was badly needed at the time, as the old favourites had become dull and uninspired. His position in the Surgical world has grown in lustre and fame ever since.

" During his years at Oxford, Sir Arthur soon showed that he was not merely a scholar but a high ranking athlete. He annexed some University records, notably the 220 yards hurdles, and he broke even time to win the Oxford and Cambridge 100. He then represented his home country and captained the New Zealand team at the Paris Olympics of 1924, when he won the Bronze Medal in the 100 metres. He was again the New Zealand captain at Amsterdam in 1928 and managed the team at Berlin in 1936. He also put up some fine performances in the international matches with the American

Universities in the United States. Thereafter, he continued his interest in athletics as a member of the Olympic Committee and Chairman of the Empire Games Federation. In conjunction with the famous half-miler, D. G. A. Lowe, he published a textbook entitled *Athletics* and wrote many articles on this subject.

" In the second World War he attained the rank of Brigadier in the Royal Army Medical Corps and was Consulting Surgeon to the 21st Army Group.

" As a result of sterling work in his wide field of interests he became very well known and highly respected in the world of British Surgery. He had been appointed Surgeon to His Majesty's Household in 1937 and, after the war, honours came to him in quick succession.

" The famous French surgeon of the 16th century, Ambroïse Paré, was, in the space of less than forty years, surgeon in succession to five Kings of France, but in those days French monarchs were extremely short lived. Sir Arthur was made Surgeon to His Majesty the late King George VI in 1946 and, on his death, Her Majesty Queen Elizabeth appointed him her Sergeant Surgeon in 1952. Long may they both live!

" Last year he was chosen by his fellows on the Council of the Royal College of Surgeons to follow Sir James Paterson Ross as their President, but he was also elected by the general body of the medical profession President of the British Medical Association, an unique honour, which I believe has never before been achieved by any man, but which serves to point the trust and affectionate regard in which he is held by the whole of the medical profession.

" We are indeed pleased to welcome Lady Porritt to the College, and we feel sure that her presence here on this occasion must materially contribute to the comfort and satisfaction of Sir Arthur.

" Distinguished surgeon, scholar, teacher, author and athlete: such is the man I present to you, Mr. President, that you may confer on him the highest honour we have in our power to bestow, the Honorary Fellowship of the Royal Australasian College of Surgeons."

In presenting the diploma the President of the Royal Australasian College of Surgeons added some words of his own, namely:

" And now, Mr. President, may I say how greatly we appreciate your acceptance of this Honorary Fellowship. We are grateful for the circumstances which have made it possible for us not only to confer this Honorary Fellowship, but also to welcome Lady Porritt and yourself to the Headquarters of our College.

" I would like to stress the fact that you have just become an Honorary Fellow of a College of whose Fellows nearly one thousand are also Fellows of the College over which you so admirably preside.

" May we ask you to take back with you to Lincoln's Inn Fields the most sincere good wishes of this College."

The President of the Royal College of Surgeons of England then replied as follows:

" Mr. President, Members of Council,

" To express adequately my appreciation of this great honour you have conferred upon me is indeed difficult. I value it as an expression of goodwill towards the President of a Sister College, all the more so, Sir, in that I have received it at your hands: those of another Rhodes Scholar. It is surely a unique happening that three Rhodes Scholars should be occupying the Chair of three Colleges of Surgeons at the same time (the other partner in the triumverate being Jack Douglas of Johannesburg). But I also value the honour personally as a New Zealander and an Australasian. If my memory does not fail me, one of the original five stars of your flag represented New Zealand (probably the big one!), and despite all the friendly partisanship that exists between the Australians and New Zealanders, there is a common bond that has been increasingly strengthened over the years—a bond that is indelibly imprinted in history through the term ANZAC.

" During the past twelve years I have seen a number of Honorary Fellowships given. I have on occasion myself given the required citation and in the last six months I have in fact conferred such an honour twice on behalf of my College. But for the first time to-day I have been on the receiving end and this fact is for me a very heartwarming one which I shall never forget as long as I live.

" The relationship of our two Colleges is surely one of the happiest that could exist —and I think I would be right on this occasion in saying that much of that happiness in recent years has developed through the personal efforts of one man—whom we all deeply mourn—that Master of Surgery, oratory, diplomacy and friendship, Gordon-Taylor. As he was to most of you, so he was to me, a great and good friend.

" The first dinner I gave in the President's Lodge in Lincoln's Inn Fields was attended by an Australian Fellow and his wife, a New Zealand Fellow of both our Colleges and his wife, G.-T. and the man who painted that magnificent portrait that will hang outside this room—James Gunn.

" That spirit of mutual understanding and common purpose is one we in both Colleges must maintain and enhance. On this trip of mine I have been stimulated to learn of the spreading sphere of influence of this younger College into other less developed countries. The very fact of this widening vista to my mind underlines the vital necessity of yet closer links with the senior College—offering as it does unique and unparalleled opportunities of clinical and scientific surgery.

" The essential qualification for greater responsibility is greater experience. I should hate to think of Lincoln's Inn Fields without its always appreciative and appreciated quota of Australians—and I believe firmly that this feeling is reciprocated.

" I was delighted too that your College, Sir—now my College also—saw fit to re-enter the International Federation of Surgical Colleges—a body so closely allied to the ethics and standards of surgical education and practice throughout the world—a body that needs Australasian support.

" To mark the occasion I bring you with the best wishes of my Council two prints of the College as it was about a hundred years ago. I can assure you that in Lincoln's Inn Fields to-day, the College which so many of you here will remember is flourishing; that its new buildings are within sight of completion; that its activities are now protean and intense; and that it is actively developing and promoting both the art and science of surgery. You can be very sure that any Fellow of the Australasian College will always find the warmest welcome at any time within its portals.

" May I again express to you, Sir, and your Council my deep gratitude for the honour you have done me to-day and assure you that I shall spare no effort as a Fellow of both Colleges to advance their mutual well-being and activities."

The ceremony was followed by a Reception attended by a large number of Fellows of the Australasian College and their wives.

THE CARTWRIGHT PRIZE

THERE WAS A printing error in the May 1961 issue of the *Annals* in the subject for the essay to be submitted in competition for the Cartwright Prize for the quinquennium ending 31st December 1965. The correct title should be " The Dental Management of the Haemophiliae and Allied Blood Conditions ".

PASSAGES FROM THE NOTEBOOKS OF SIR FREDERICK TREVES, Bt.

Recently the College was presented by the Dowager Lady Rigby with some notebooks of Sir Frederick Treves, Bt., G.C.V.O., F.R.C.S. (1853–1923), through the good offices of Sir Cecil Wakeley, Bt. Sir Frederick was succeeded as Consulting Surgeon to the London Hospital and as Serjeant Surgeon to King George V by Sir Hugh Rigby, Bt., K.C.V.O., F.R.C.S. (1870–1944), to whom he gave these notebooks. They were written by Sir Frederick Treves in his own copper-plate handwriting, and contain accounts of notable occurrences in his life. As an introduction to these he writes:

> "I have been repeatedly pressed by certain friends to write an account of notable episodes in my professional life. The following incidents, reported with the most precise accuracy, will show how utterly impossible it is to carry out this suggestion. I have, therefore, abandoned it."

Three cases were described in the notebooks, the first of which is published here. It is hoped to publish the second one in a future issue of the *Annals*.

I. The Case of Sir John Millais

THE OPERATION I performed on Sir John Millais, President of the Royal Academy, was carried out under circumstances of some disorder. Sir John had been ill for many months with cancer of the larynx. The trouble appears to have first shown itself about October 1892, but I did not see the patient until I was summoned to operate upon him. He was under the care of Mr. Hames, an old friend of mine and a particularly able practitioner.

Late on Sunday evening, 10th May 1896, Hames called upon me to say that he would probably require me to perform a tracheotomy on Sir John at any moment, adding that the patient was in a critical condition, that he had great difficulty in breathing and had already experienced attacks of suffocation which were very alarming. Hames proceeded to explain why I was called upon at this late hour of the day. Millais had been treated for the laryngeal trouble by a well known throat specialist. Hames had formed the impression, correctly or incorrectly, that this gentleman was a little afraid of the operation and was disposed to leave it in the hands of another surgeon. How far Hames was justified in his surmise I never knew. Anyhow I placed myself at Hames's disposal and assured him that I was prepared to operate provided that the throat specialist was not available or was no longer in attendance.

Later I received a summons to come at once to No. 2 Palace Gate. I went without a moment's delay. The specialist had been sent for, but the messenger, on reaching his house, was told that he had gone out to supper. He then went to the house at which he was said to be supping, but found that he had already left. It was now past midnight. The messenger called once again at the surgeon's house but was informed that he had not returned. He then came on to me.

I reached No. 2 Palace Gate somewhere about 1.45 on Monday morning. There was no sign of life in the street and I feared that the reckless clatter of my cab would arouse the whole suburb. The great house, heavy,

melancholy and unhomelike, is well known. It appeared to be in darkness. Before I could ring the bell Hames opened the door to me and beckoned me in, as if I had been a conspirator. I entered a large cavernous hall that suggested the vestibule of a closed museum. It was dimly lit, so that I could only appreciate a bare, marble floor, some statuary and a chilly staircase leading upwards into nothingness. I had expected to meet those harried relatives, pale with panic, who often lie in wait for the surgeon, when a momentous operation is impending, who seize his arm and gasp forth tremulous questions before he has hardly passed the threshold. But the hall was empty and impressively silent. There was not even in the background an awed servant to be seen.

Hames and I walked across the hall on tiptoe. I have often wondered why we did this and can only surmise it was on account of the sepulchral stillness of the place. Millais was lying in a room on the ground floor to the left of the hall. This room had a large window looking onto the road. It was evidently not originally a bedroom and bore, therefore, that inappropriate and desecrated appearance which a library or smoking room presents when a bedstead and its belongings are thrust into it. The room was ill lit, for it had neither gas nor electric light, while the lamps and candles threw prodigious shadows on the wall. It was an unrestful place for a man to sleep in, but it was the room Millais liked. The bed was against the wall that faced the window and was so placed that it stood out into the room among the protesting, incongruous furniture. It was a narrow bed and so extremely low that it seemed to be almost on the ground.

On entering the room poor Millais' position was at once made evident by his terrible breathing. There is no human sound more pitiful than that tense whistling in the throat of a suffocating man. It was as rhythmical and monotonous as a labouring pump, as hopeless as a cry of thirst in a desert. In this despairing struggle for breath the air had to be drawn through a tube narrowed to the size of a straw. Through this slowly closing chink the air hissed with every upheaval of the mighty chest. Propped up in bed by a pile of crumpled pillows was the familiar form of Millais, the form of a still fine, handsome man. His face was livid as that of a drowning man; his lips were black; crawling veins stood out on his temples; sweat poured from his brow; his eyes seemed forced from his head. He was speechless. His aspect was one of desperation and yet of grim courage. The bed was in savage disorder, a mere hummock of contorted sheets among which lay two or three handkerchiefs which had been squeezed into balls.

When I went to Millais he looked at me as if I conveyed some ray of hope. He pointed to his throat and then held his hand out towards the room as if to say—give me this air to breathe. His pulse was so rapid as to be uncountable. I told him he would soon be out of his trouble.

I felt in a moment that the expression was unfortunate as he might die under the operation.

I turned to Hames and asked him " Where was the nurse? " He said there was no nurse. Sir John objected to have a nurse. Moreover the throat specialist had arranged to bring a nurse when he came to operate, but he had failed at the last. Up to the present there had indeed been no need for a nurse. I found that Lady Millais and some of the family were in the house and suggested that they should be called, but Dr. Hames said " No ". The extreme attack had developed after the family had retired for the night. They retired with the assurance that nothing would, in any case, be done before daylight on Monday. Moreover, Millais objected to fuss and was most anxious that his family should neither be alarmed nor disturbed under any circumstances.

When I was enquiring about a nurse I was aware of an elderly vague woman in the room who was apparently a housemaid. She stood in the shadow like a sentinel, immobile and numb. She was the most purposeless and indefinite person I have ever met. I can only recall that she was elderly; but otherwise she was without form and void. She seemed incapable of expression and of movement and never uttered a sound during the whole of the time I was occupied in the room. She was spoken of as " the woman " and that was all she was.

Time was very pressing. I took out my instruments and placed them on a tray, spreading them on a towel I had found adrift on a bureau. The bed was so low that I had to place the tray on the floor by the side of the bed and at the feet of the strange woman. She looked at the white towel and the pieces of steel upon it as if they were the paraphernalia of a conjuror. If I had coiled up a live cobra on the towel I do not think she would have moved.

Millais was now *in extremis*. Hames was preparing to give chloroform. He stood behind the head of the bed, between it and the wall. As light was necessary I told the ineffectual woman to kneel on the floor, on the other side of the bed, and to hold a lamp on a level with the patient's face. This she did with the indolent precision of a mesmerized person and the stolidness of a deaf-mute.

All was now ready. It would be futile to say that there was not a minute to be lost. It was a question of seconds, not of minutes. I knelt on the floor, by the side of the bed, with my knife in my hand. I should have liked an assistant. I should have liked the aid of sponges and other appurtenances of an operation, but this procedure was as informal as an operation carried out on a bare heath at the dead of night.

In giving the anaesthetic Hames used an inhaler which consists of a rigid face-piece into which the chloroform is pumped through a tube by means of a rubber ball squeezed by the hand. Hames was very flurried and perturbed by long hours of anxiety. The intense need of haste and the dreadful struggles of the suffering man only added to his discomfort.

I was waiting on my knees for the opportunity to begin. The patient was difficult to control. I was afraid that with his frenzied hands he would hurl aside the lamp or strike the knife out of my grasp. I had only one hand free, while the indefinite woman was as useless as a somnambulist.

Just as I thought that the right moment had come I noticed, to my horror, that the tube which connected the chloroform bottle with the mask had become detached and that Hames, wholly unconscious of this disaster, was merely pumping chloroform into the room. As I pointed this out Millais fell back apparently dead. The noise in his throat ceased and his hands fell limp. In his last struggle he had slipped, pillows and all, nearly off the bed and indeed his right elbow touched the floor. I at once opened the windpipe and passed the tube into the trachea without difficulty.

I was aglow with my good fortune but, almost at the same moment, was struck cold by the sickening fear that it had come too late; for the chest never moved and no breath entered through the tube. Surely he was dead.

It has been stated—on no sound evidence—that through the brain of a drowning man will flash a lightning vision of his whole past life. It may be so; but I can testify that through a surgeon's mind, at a moment such as this, will rush the vision of a future as vivid as any past can be. I could picture the sobbing relatives gazing at me with reproachful eyes; could hear, in the world beyond, sour whisperings about " the unfortunate incident " and, above all, could see a heated newsboy hurrying through the street with a fluttering placard in explosive capitals—" Sudden death of Sir John Millais ".

I told Hames to commence artificial respiration while I held the tube in place. He acted promptly and after the first pressure on the thorax was relaxed Millais took a deep breath, a full, generous draught of air, the first he had drawn for many a day. I also drew a deep breath and with almost the same sense of relief for my work was done.

While Hames was arranging the tape with which to hold the tube in place I had a moment in which to realize the scene about us. Both he and I and the patient were practically on the floor, like three people in a street fight. There were crimson patches of blood on the crumpled sheets. Everywhere was intense disorder. The bed itself was contorted as if by a whirlwind, the room was still and full of shadows, a clock was tolling the hour of two. Had anyone looked in at the door it must have appeared that some dreadful murder was in progress and that the victim, although alive, was already speechless.

There was one other feature in the scene which stands out in my mind as the most vivid and most strange at all. When the tube had been secured and the helpless man dragged up again to his place on the bed the ghostly woman—who had been as still as an enchanted figure—placed the lamp very deliberately on the floor, and proceeded to crawl slowly out of the room on her hands and knees. The door was ajar and she crept out into the hall like an uncouth pantomime dog. She uttered no word; made no

sound and was never seen again. I think she might have crawled down into some black basement and fallen asleep against an unopened door. I asked Hames about her the next day but he knew nothing. He seemed almost to doubt her very existence. So shadowy was she that she might have been the evil spirit that had been cast out of the man crawling away from the scene of his disquietude. Poor soul, she had done her best gallantly enough; but I doubt not the memory of that dreadful hour haunted her for the rest of her days. I should have liked to have heard the story she told to the household as they came yawning downstairs when the morning dawned.

Millais, who had been in the actual Valley of the Shadow of Death, soon came to himself. Before I left he beckoned me to his bedside. I came and put a hand on his forehead. He took my other hand in his and squeezed it. It did me good. I had passed through a troubled time, but that grip of the hand repaid it all.

APPOINTMENT OF FELLOWS AND MEMBERS TO CONSULTANT POSTS

B. W. M. BUSHELL, F.R.C.S.	E.N.T. Surgeon, West Middlesex and Brentford Hospitals and Teddington, Hampton Wick and District Hospital.
B. CASHMAN, F.R.C.S.	Orthopaedic and Traumatic Surgeon, Bedford General Hospital.
R. C. HALLAM, M.R.C.P., M.R.C.S.	Clinical Pathologist, Bedford General Hospital.
M. P. A. MENON, F.R.C.S.	Clinical Assistant, Christian Medical College and Hospital, Vellore.
N. L. MILLS, M.R.C.S.	Radiologist, Royal London Homœopathic Hospital.
A. G. POLLEN, F.R.C.S.	Orthopaedic and Traumatic Surgeon, Bedford General Hospital.
A. J. ROOK, M.D., M.R.C.P., M.R.C.S.	Dermatologist, Bedford General Hospital.

ANATOMICAL MUSEUM

IN THE ANATOMICAL MUSEUM during June, there will be a demonstration of museum display techniques.

THE TRAINING OF SURGEONS

THE COUNCIL OF the College has established a post of Adviser in Surgical Training, the first holder of which is Sir Clement Price Thomas, K.C.V.O. Some of the duties of the Adviser were originated by Sir Gordon Gordon-Taylor, and are being continued by Sir Clement; these include advice to young surgeons regarding their future surgical training.

In Memoriam

PROFESSOR JULIAN TAYLOR, C.B.E., M.S., F.R.C.S., Hon. F.A.C.S. (1889–1961)

The Address given by Mr. A. J. Gardham, F.R.C.S., at the Memorial Service held at St. Pancras Church on Wednesday, 10th May 1961

WE ARE HERE to pay our tribute to Julian Taylor, whom we all knew as a gallant and straightforward man who lived a life full of effort and achievement. Behind this there is a story of a complex personality, and there were so many sides to Julian's character that even those who knew him well were left with a feeling that they had seen only a part of what was there. Those who knew him less well saw virtually nothing. One thing

Julian Taylor

certain is that Julian was a dedicated man; dedicated to the exercise of his profession and to the maintenance of its highest traditions. Like all dedicated men he sometimes saw enemies where only friends existed, and many of his erstwhile foes were later numbered among his firmest friends.

Julian grew up in an atmosphere of wide knowledge and critical appreciation. This much was clear to those who knew him in his early days and had the privilege of seeing something and hearing perhaps a little more of the family circle. At University College he found an atmosphere which suited him well, and by the time that he reached the hospital his intellectual capacity was clear and so was his intolerance of cant and his detestation of false values. The first World War gave him the opportunity to show his qualities as a man of action and he came back to U.C.H. with

his sabre flashing and an endearing readiness to tilt against windmills. I think U.C.H. in those days gave him all he wanted. He had the intellectual stimulus of association with Trotter and Barrington, both of them great thinkers in very different ways, the stern realism of Gwynn Williams, and the challenge of the newly emerging scientific departments. To Julian, Trotter could do no wrong. The rest he examined carefully, and catalogued their virtues and failings with a mathematical accuracy which some found a little trying.

About this time, another characteristic began to emerge. Julian, a merciless and fearless critic of his equals and seniors, began to show an understanding of his juniors and a tenderness for their failings. This characteristic persisted throughout Julian's life, and perhaps my best qualification for speaking now is that he looked after me when I was a young man, and I am therefore able to give thanks on behalf of the many young men whom he laughed at and criticized to their faces, and praised and defended behind their backs. His generosity towards his juniors knew no limits; did you want a car? take his. Did you want a holiday? share his. Did you need a house for this, that, or the other purpose? his was at your disposal.

With his equals and his seniors he was never able to move on quite the same easy lines and the quick cross-currents of his mind sometimes earned him the reputation of being cornery. This I am prepared to admit, but it made me sad to see him described in an appreciation as " opinionated ". Julian had faults but this was not one of them. He had opinions, generally for very good reasons, and his instinct made him defend them strongly. At the same time his intelligence told him that they might be wrong, and few people were more ready than Julian to consider this unpalatable possibility.

In 1926 Julian married a charming and graceful wife. A year later he was on the staff at U.C.H. and this was soon followed by his appointment to Queen's Square. Thereafter came an increasingly busy practice and a house in Portland Place which was the envy of all his friends. The good years followed and it is tragic that they were so few. During these years Julian had time and energy for everything.

At U.C.H. he filled to perfection the part of a consultant in the middle period of life. Apparently quite tireless, he was in and out of the place at all hours, tackling every problem which came his way with ability and zest, and all the while teaching, sometimes by precept to the young, and by example to us all. His thought was clear and his action quick, and there are few of us, young or old, who have not at some time or another turned to Julian for help when things were difficult.

Out of hours, sailing, of course, was his greatest love, but he had time and zest for other student activities and, at the same time, he did great work as Secretary to the Association of Surgeons.

Then the war came and Julian threw his life into the melting pot. I know well that this was no impulsive act; it was done with all the clear incisive reasoning that Julian put into his clinical problems, and it was a willing, cold-blooded sacrifice.

The rest of the story would be a tragedy if it were not for the picture which it gives of an indomitable man, suffering a series of staggering blows, and rising fresh each time to make a new and better effort.

What Julian suffered as a prisioner of war only he knew, but I was his friend, both before and after the war, and I think I can guess. When he started to re-make his life he found that the outlook in neurological surgery had changed, and, in spite of his intellect and his great skill, he never led the van in this speciality. This was largely because, in the earlier days, he had refused to abandon general surgery, and it is interesting and comforting to know that, although this decision prevented him from attaining greatness as a neurosurgeon, it left him qualified for the two greatest achievements of his life. The first was his work in the prison camp at Singapore and the second his work in Khartoum. I must say a little of both of these later.

Facing the fact that neurosurgery was now an interest rather than a calling, Julian returned to his old way of life with undiminished zest but fewer physical resources. With a practice building up for the second time, and the tremendous encouragement given by his election to the Council of the Royal College of Surgeons in 1946, it seemed, for a time, that the misfortunes brought by the war would soon be forgotten. Even the United Hospitals Sailing Club at Burnham was again flourishing under his skilful guidance.

Just as it seemed that Julian's troubles were over, his wife, who meant so much to him, developed the illness which finally caused her death. Julian withdrew himself a little more and that was all, but I think that from this time his attitude to life underwent a change. I believe he felt that Fate had thrown out a final challenge which he proposed to take up and to win. This he did and it must have given him great satisfaction.

Besides the work as a friend and teacher of the young, which went on continuously, Julian's life contained two notable achievements. In the prison camp at Singapore he stood as a towering example of the victory of man over circumstances. It is not enough to speak of the gratitude of fellow prisoners. His work went far beyond that and it will stand for ever as a shining example to the profession, the nation, and to mankind.

His second great achievement was his work in Khartoum. When I say this, I do not belittle the work which he did at U.C.H. and in the Royal College of Surgeons after the war, but this was work which could have been done by others. Julian's achievements as Professor of Surgery in Khartoum were of a different order as they were an individual contribution given in the closing years of a life which might, if he had chosen, have been devoted to a well-earned rest.

In Khartoum, Julian started almost from the base line and set out to create a service on the British system. He meant the service ultimately to be run by the Sudanese for the Sudanese, and he laboured unceasingly to make sure that it would incorporate all which he thought was good in the British system. For this purpose he saw that it was necessary that some of his more promising assistants should see the British system at work in this country, and it gave him great pleasure when he was able to introduce them to posts in British hospitals. An appreciation from one of his assistants has appeared in a medical journal since Julian's death, and I believe it would have given him more pleasure than many tributes from higher sources. His work in the Sudan was very dear to his heart. It is, and will continue to be, a blessing to the Sudan and it ranks high as an achievement for British surgery.

PROCEEDINGS OF THE COUNCIL IN MAY

AT A MEETING of the Council on 11th May 1961, with Sir Arthur Porritt, President, in the Chair, a resolution of condolence was passed on the death of Professor Julian Taylor, who had been a Member of Council since 1946, and was Vice-President in 1954–56.

Dr. E. Rohan Williams, F.F.R., of St. Mary's Hospital (former co-opted Member of Council) was admitted as a Fellow by election.

Mr. T. A. Ogilvie, F.R.C.S.Ed., of Colchester, was elected to the Fellowship *ad eundem*.

A Certificate of Honourable Mention for the Jacksonian Prize for 1960 was presented to Mr. H. Hamilton Stewart, Fellow, of Bradford.

The Cartwright Prize for 1960 was presented to Professor G. L. Howe of Newcastle, Fellow in Dental Surgery and Member, and a Certificate of Honourable Mention for his Cartwright essay to Mr. H. P. Cook, Fellow in Dental Surgery, of the Middlesex Hospital.

The Begley Prizes were awarded to Miss Susan Key of the University of Liverpool and Miss Rosemary Raymonde Norton of Guy's Hospital Medical School on the result of the recent examination in Surgery for the Membership of the College.

The President was appointed as representative on the Governing Body of the British Postgraduate Medical Federation for the year 1961–62.

Mr. A. Hedley Whyte, Fellow, was re-appointed as representative on the Council of King's College, Newcastle-on-Tyne.

The Laming Evans Senior Research Fellowship in Orthopaedic Surgery of Mr. R. G. Smith, Fellow, was renewed for a second year from 19th April 1961.

Diplomas of Membership were granted to 175 candidates, who were successful in the recent Final Examination of the Examining Board in England.

One Diploma in Anaesthetics was granted, jointly with the Royal College of Physicians.

The following hospitals were recognized under paragraph 23 of the Fellowship regulations:

Hospitals	Posts Recognized		
	General (6 months unless otherwise stated)	Casualty (all 6 months)	Unspecified (all 6 months)
London—Acton Hospital		Cas. Regr.	
London — Royal Northern Hospital (additional)			Regr. (Orth.)
Macclesfield Hospital			Regr. (Orth.)
Carshalton—Queen Mary's Hospital for Children (additional and rearrangement of duties)			S.H.O. (Orth. and Gen.) (*additional*) S.H.O. (E.N.T. and Gen.)
Romford—Rush Green Hospital (redesignation)	Senior Surg. Regr. Junior " " H.S.	redesignated as	Surg. Regr. S.H.O. H.S.
Workington Infirmary (additional)	H.O. Surg. Regr.		
Bulawayo — Mpilo Central Hospital	3 Resident Surg. Offrs.	Resident Cas. Offr.	
Saudi Arabia — Dhahran Health Centre and Hospital	4 Junior Surgeons (6 months General: 6 months Casualty)		

THE COLLEGE APPEAL

It was thought that Fellows might like to know the progress of the Appeal to date. This Appeal was launched in March 1959, and the totals given below do *not* include gifts or subscriptions by Fellows prior to that date, or compulsory annual subscriptions.

The grand total of the Appeal Fund stands at £2,566,179 11s. 9d.,* and of this a total of £30,085 14s. 8d. has been voluntarily contributed by Fellows, Fellows in Dental Surgery and Fellows of the Faculty of Anaesthetists.

This amount is subdivided into £19,538 10s. 6d. donated by some 276 Fellows (out of a possible total of 5,100 of whom another 761 pay a compulsory annual subscription to the College consequent upon the passing of the Bye-Law under Section 14 of the Regulations in December 1957); £2,504 donated by some 68 Fellows in Dental Surgery (out of a possible total of 348, of whom another 75 pay a compulsory annual subscription); and £8,042 5s. 2d. by some 121 Fellows of the Faculty of Anaesthetists (out of a possible total of 411, of whom another 262 now pay a compulsory annual subscription).

Any further contributions from Fellows, Members and Associates will be greatly appreciated by everyone concerned with the Appeal.

* This sum includes the recent promise by the Wolfson Foundation, as reported on page 366 of this issue of the *Annals*.

OSLER CLUB

THE EVENING OF 7th April was the occasion of a very pleasant ceremony when the 187th meeting of the Osler Club was held at the College and 95 members and guests dined most excellently in the Edward Lumley Hall. There was an especial feeling of warmth and friendliness, for the purpose and business of the meeting was to pay tribute to Sir

Sir Zachary Cope

Zachary Cope, first President of the Club, on his eightieth birthday, the actual date of which was 14th February. The present President, Mr. Dickson Wright, welcomed the guests, these including representatives of the firms who have published the many and varied writings of the guest of honour. Speaking on their behalf, Mr. Charles Macmillan, Managing Director of Messrs. E. and S. Livingstone, voiced the feelings of all when he spoke of the high regard in which Sir Zachary was held; here indeed was a man loved and respected, a good counsellor, a trusted friend, of whom no derogatory word could be spoken. It was a rare privilege to be able

to express, rather than merely recall, an appreciation of the qualities and achievements of one of the most distinguished members. Sir Zachary gave more than a formal reply to the toast; he unfolded for us the fascinating architectural history of the College in the early years of the nineteenth century, when it first embarked upon monumental building.

DONATIONS

DURING THE LAST few weeks the following generous donations have been received:

Appeal Fund—Contributions

£5,000	Cadbury Brothers Charitable Fund
£4,290	Unilever, Ltd. (further gift)
£1,050	London Brick Co. Ltd.
£500	The Bank of England (further gift)
	Public Trustees (from the James White Estate)
	Metal Box Charities
£250	Bristol Aeroplane Trust
	Baring Bros. Ltd.
	Schroder Charity Trust (further gift)
	J. Bibby & Sons, Ltd. (further gift)
£200	Equity & Law Charitable Trust (further gift)
	The Northern Employers Assurance Co.
£163	The Yorkshire Insurance Co. Ltd. (further gift)
£150	Wiggins, Teape & Co. Ltd. (further gift)
£105	T.W.W. Limited
	Moynihan Club, Birmingham
£100	Littlewood Charitable Trust (further gift)
	Friend's Provident & Century Life (further gift)
	Mrs. M. Sassoon
£81 12s. 8d.	Sea Insurance Co. Ltd. (further gift)
£50	S. Japhet & Co. (further gift)
£34 10s. 0d.	V. Masraff, Esq.
£26 5s. 0d.	William Cowlin & Son, Ltd.
£25	Farley's Infant Food, Ltd.
£10 10s. 0d.	Mable Peatfield Charities Co.
£10	Bell Woodworking Co. Ltd.
£5 5s. 0d.	J. M. Shand, Ltd.
£5	Mrs. M. Vigar
£3 3s. 0d.	Blight & White, Ltd.
£2 2s. 0d.	Coates Bros. & Co. Ltd.
£1	H. C. Beaumont, Esq. (further gift)

Pharmacology Department

£1,000	May & Baker, Ltd.

Research Department of Anaesthetics

£1,000	May & Baker, Ltd.
£750	The Butterly Co. Ltd. (further gift)

Appeal Fund—Covenant

£500 p.a. for 7 years less tax	William Warner & Co. Ltd.

DONATIONS

Voluntary subscriptions and donations by Fellows

The following Fellows of the College have generously given a donation or have undertaken to make a voluntary annual subscription under covenant:

R. H. R. Belsey, F.R.C.S.
H. W. C. Fuller, F.R.C.S.
T. K. Lyle, C.B.E., F.R.C.S.
H. Neame, F.R.C.S.
A. G. Parks, F.R.C.S.

McIndoe Memorial Fund:

£7,000	Jack Cotton First (1953) Charitable Trust (first payment of a total of £50,000)
£21	The Worshipful Company of Barbers

Through the good offices of Dr. T. D. Rees, M.D., of New York:

$25	The Cleveland Trust Company
	Gerald M. Grey, M.D.
	J. J. Longacre, M.D.
	Matthews A. Pilling, M.D.
	Richard B. Stark, M.D.
$10	Jerone R. Klingbell, M.D.
	John R. Lewis, Jnr., M.D.
	Jack L. and Julian Wirt Teasley
	Thomas Cronin, M.D.
$5	Frederick J. McCoy, M.D.

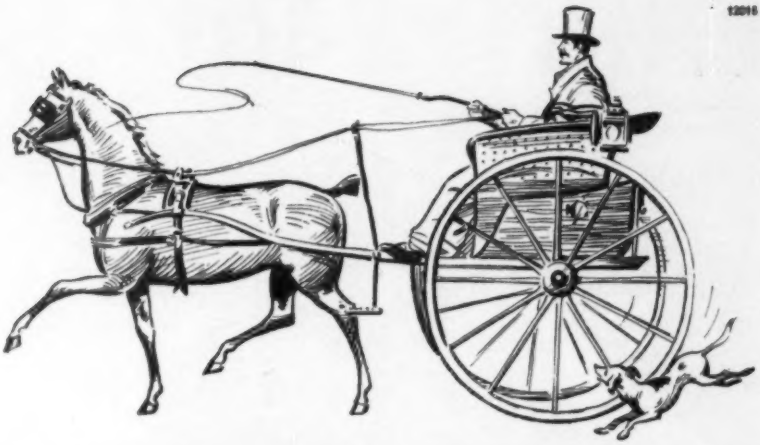
DIARY FOR JUNE

Thur.	15		Pre-Medical Examination and D.L.O. Examination (Part I) begin.
Fri.	16		Election of Fellows to the Board of Faculty of Dental Surgery. Dental Lectures and Clinical Conferences end.
Wed.	21		First L.D.S. Examination begins.
Thur.	22		First Membership Examination and D.L.O. Examination (Part II) begin.
Tues.	27		Final Membership Examination begins.
Wed.	28	4.00	Meeting of the Hunterian Trustees.
		5.00	Miss J. Dobson—Arnott Demonstration—John Hunter's animals and friends.
		5.00	Board of Faculty of Anaesthetists.

DIARY FOR JULY

Tues.	4		Final F.D.S. Examination begins.
Wed.	5		D.M.R.D. Examination (Part I) and D.M.R.T. Examination (Part I) begin.
Thur.	6	11.00	Election to Council.
Tues.	11		Final F.F.A. Examination begins.
Wed.	12		D.O. Examination and D.T.M. and H. Examination begin.
		5.00	Professor G. W. Milton—Hunterian Lecture—The behaviour of gastric epithelium under various conditions.
Thur.	13		D.I.H. Examination and D.Phys. Med. Examination (Part I) begin.
		10.30	Quarterly Council—Election of President, Vice-Presidents and Lecturers.
Thur.	20		D.Phys. Med. Examination (Part II) begins.
Fri.	21	3.00	Professor A. I. Darling—Charles Tomes Lecture—The selective attack of caries on the dental enamel.
		4.00	Annual General Meeting and election of Licentiate to the Board of Faculty of Dental Surgery.
Sat.	22		Board of Faculty of Dental Surgery.
Fri.	28		Basic Sciences Lectures and Demonstrations for Dental Students end.

12018



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C.R.F. 94, Imperial Cancer Research Fund, 49 Lincoln's Inn Fields, London, W.C.2

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